IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. MYLAN INC., MYLAN PHARMACEUTICALS INC., MYLAN GMBH and MYLAN N.V., Defendants.	C.A. No. 17-cv-01235-MRH ***Electronically Filed***

DECLARATION OF GEORGE GEORGIOU, PH.D. IN SUPPORT OF MYLAN'S RESPONSIVE CLAIM CONTRUCTION BRIEF REGARDING U.S. 9,643,997 B2

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I. INTRODUCTION.

1. I, George Georgiou, Ph.D., have been retained to testify as an expert in this case on behalf of Mylan Inc., Mylan Pharmaceuticals Inc., Mylan GmbH, and Mylan N.V. (collectively, "Mylan" or "Defendants") in the above-captioned action. I have personal knowledge of the facts set forth in this Declaration, and I believe I am competent to testify to the same.

2. I understand that I am providing this Declaration in support of Mylan's Responsive Claim Construction Brief and in response to Plaintiffs Amgen Inc.'s and Amgen Manufacturing Limited's (collectively, "Amgen" or "Plaintiffs") Opening Claim Construction Brief (ECF No. 106), inclusive of the Declaration of Richard C. Willson in Support of Amgen's Opening Claim Construction Brief (ECF No. 108).

3. For the purpose of this declaration, I have been asked to focus on Amgen's U.S. Patent No. 9,643,997 B2 ("the '997 patent"), which I understand Amgen has asserted against Mylan in this case. I understand, however, that Amgen has asserted a second patent against Mylan, U.S. Patent No. 8,273,707, and that I may be called to testify regarding that patent at a later date.

4. In forming the opinions set forth in this declaration, I have reviewed, among other things, the '997 patent and prosecution history, the parties' Joint Disputed Claim Terms Chart (ECF No. 100-1), Amgen's Opening Claim Construction Brief ("Amgen Br.") as well the Declaration of Richard C. Willson in Support of Amgen's Opening Claim Construction Brief ("Willson Decl."). In this declaration, I provide, among other things, my opinions regarding the person of ordinary skill in the art's understanding of the terms used in the '997 patent claims. Moreover, I provide my opinions in response to certain comments and assertions made by Amgen and/or Dr. Willson.

II. QUALIFICATIONS.

5. I am the Laura Jennings Turner Chair in Engineering at the University of Texas at Austin and serve as a Professor in the departments of chemical engineering, biomedical engineering, and molecular biosciences at the University of Texas at Austin.

6. I am trained as both a chemical engineer and molecular biologist and the focus of my research is on the discovery and development of protein therapeutics and the analysis of human adaptive immune responses.

7. In 1981, I graduated from the University of Manchester (UK) with a Bachelor of Science degree in chemical engineering. In 1983, I earned a Master of Science degree in chemical engineering, and in 1987 I earned a Ph.D. in chemical engineering, both from Cornell University in New York.

8. From 1986-1991, I worked as an assistant professor in the chemical engineering department at the University of Texas at Austin.

9. From 1991-1994, I worked as an associate professor in the chemical engineering department at the University of Texas at Austin.

10. In 1995, I was promoted to professor at the University of Texas at Austin.

11. In 1996, I was elected fellow at the American Institute for Biological and Medical Engineers.

12. In 2003, I received the Marvin J. Johnson Award in Microbial and Biochemical Technology by the American Chemical Society.

13. In 2004, I was elected fellow at the American Academy of Microbiology and the American Association for the Advancement of Science.

14. In 2005, I was elected to the National Academy of Engineering.

15. In 2005, I was named an Endowed Chair Professor in Engineering at the

University of Texas at Austin, a position I still hold today.

16. In 2007, I was also awarded the Amgen Award in Biochemical Engineering.

17. In 2008, I was elected as one of the 100 Eminent Chemical Engineers of the Modern Era.

18. In 2011, I was elected to the National Academy of Medicine.

19. In 2014, I was named by *Nature Biotechnology* as one of the "Top 20 Translational Researchers in the world for 2013."

20. In 2015, I was elected to the American Academy of Arts and Sciences and to the National Academy of Inventors.

21. I have been recognized for my numerous contributions to science, including the invention of Ig-Seq, a powerful tool that is providing invaluable information on the sequences, diversity, relative abundance and functions of the serological antibody repertoire elicited by vaccination or infection.

22. I have also used my extensive background in protein engineering and biochemistry to invent and validate several protein therapeutics that are undergoing or about to enter clinical evaluation.

23. I have published extensively in the areas of protein therapeutics and human adaptive immune responses, with my current research focused in part on human serological and B memory repertoires following vaccination or infection and the discovery and preclinical development of human therapeutic enzymes for amino acid depletion therapy in cancer.

24. I am a named inventor on 47 issued U.S. patents, and I have published over 250 scientific papers.

25. I sit on the editorial board of the following journals: ACS Synthetic Biology,

Biotechnology and Bioengineering, Protein Expression and Purification, Journal of Biotechnology, Microbial Cell Factories, and the Oxford University Press.

26. My education and employment history are summarized in my Curriculum Vitae attached hereto as Exhibit A, which also contains a list of my publications, patents, and oral presentations.

27. My opinions are based on my personal knowledge, background, education and experience and on the materials I have considered in connection with this litigation.

28. I reserve the right to supplement or amend my opinions relevant to my understanding of the meaning of certain claim terms or phrases based on additional information obtained or in order to clarify the information provided herein, including based on any submission by Amgen or any relevant Court ruling.

III. RETENTION AND COMPENSATION.

29. Defendants have retained me as a technical expert in this matter to provide opinions related to the patent-in-suit. I am being compensated at $1,200 per hour for my services. My compensation is not dependent upon my opinions or the outcome of the litigation. I have no current or past affiliations with Plaintiffs or the named inventors of the patents-in-suit.

30. I have not testified at a trial or by deposition in the past four years.

IV. LEGAL STANDARDS APPLIED.

31. I understand that claim construction is the process by which the Court determines the meaning and scope of the terms in a claim.

32. I understand that, in general, claims are construed to have their plain and ordinary meaning as understood by a person of ordinary skill in the art as of the effective filing date of the patent application. Further, I understand that the ordinary and customary meaning of a term may be evidenced by a variety of sources, including the words of the claims themselves, the

specification, drawings, and prior art. However, the best source for determining the meaning of a claim term is the specification. It is also my understanding that extrinsic evidence such as treatises and dictionaries may also reveal the true meaning of language used in the patent claims.

33. It is my understanding that there are two exceptions to this general rule: (1) when the inventors have defined terms in the specification in a way that is not consistent with the plain and ordinary meaning of the term; and (2) when the patentee excludes, restricts or otherwise disavows the full scope of a claim term either in the specification or during prosecution.

34. Accordingly, I understand that claim terms should be determined in light of the patent's specification, prosecution history, and relevant extrinsic evidence.

35. I understand that the prosecution history of a patent is the record of the communications between the Applicant and the Patent Office that led to the issuance of the patent. It is also my understanding that claim terms should generally be construed in a manner that is consistent with the statements made to the Patent Office during prosecution. For example, I understand that when a patentee seeks to overcome prior-art based rejections by repeatedly emphasizing that a particular feature is important or critical in order to secure allowance of the claims, such statements constitute a disclaimer of claim scope with respect to that feature.

36. Further, I understand claim terms are presumed to be used consistently throughout a patent and additionally presumed to carry the same construed meaning in the same patent or related patents. Thus, where multiple patents derive from the same parent application and share many common terms the claim terms must be interpreted consistently across all patents.

V. PERSON OF ORDINARY SKILL IN ART.

37. I have been informed that the claims are to be understood from the perspective of a person having ordinary skill in the art at the time of the invention.

38. In my opinion, a person of ordinary skill in the art as of June 25, 2009, which I

understand is the earliest filing date available to the '997 patent (*see* ¶ 47 below), would have a high level of education, training and experience. More specifically, it is my opinion that the person of ordinary skill in the art to which the '997 patent pertains would have had at least a Ph.D. degree in biochemical engineering, biomedical engineering or biochemistry with specialization in the fields of recombinant protein manufacturing and purification, or a masters or an undergraduate degree in biochemical engineering, biomedical engineering or biochemistry with several years of experience in the fields of recombinant protein manufacturing and purification.[1]

* * *

39. I have reviewed Dr. Willson's definition for a person of ordinary skill in the art with respect to the '997 patent. (*See* Willson Decl. ¶ 13). I have also reviewed the definition Amgen and Dr. Willson proposed in the *Amgen v. Sandoz* matter with respect to U.S. Patent No. 8,940,878 ("the '878 patent"), which inexplicably differs from their current proposal. (Ex. 8[2], Declaration of Richard C. Willson, Ph.D., Regarding Claim Construction of Shultz et al., U.S. Patent No. 8,940,878 ("Willson *Sandoz* Claim Construction Decl."), *Amgen Inc. et al. v. Sandoz Inc. et al.*, No. 14-cv-04741-RS (N.D. Cal.) (Apr. 22, 2016) (ECF No. 172-2)). In my opinion, the level of knowledge and experience for the "person of ordinary skill in the art" would be identical for both the '878 and '997 patents. I therefore disagree with Amgen and Dr. Willson's attempts to propose different definitions.

40. Notwithstanding my disagreement, my opinions set forth in this declaration would

[1] For example, in my opinion, this high level of education and experience would include a person with a Ph.D.; a Master's degree plus 3-5 years of experience; or a Bachelor's degree plus 7-10 years of experience in the relevant field.

[2] I understand references to numbered exhibits (e.g., Ex. 1) herein are to exhibits to Mylan's Identification of Extrinsic Evidence Pursuant to LPR 4.3(b), filed concurrently herewith.

not change if either of their definitions was adopted.

VI. TECHNOLOGICAL BACKGROUND.

41. Chromatography refers to a set of techniques for the separation of different components in a mixture. A solution containing a mixture of substances or components is applied to or allowed to travel through a material called a resin or matrix. The matrix binds certain substances but not others, which results in the separation of the substances in the mixture.

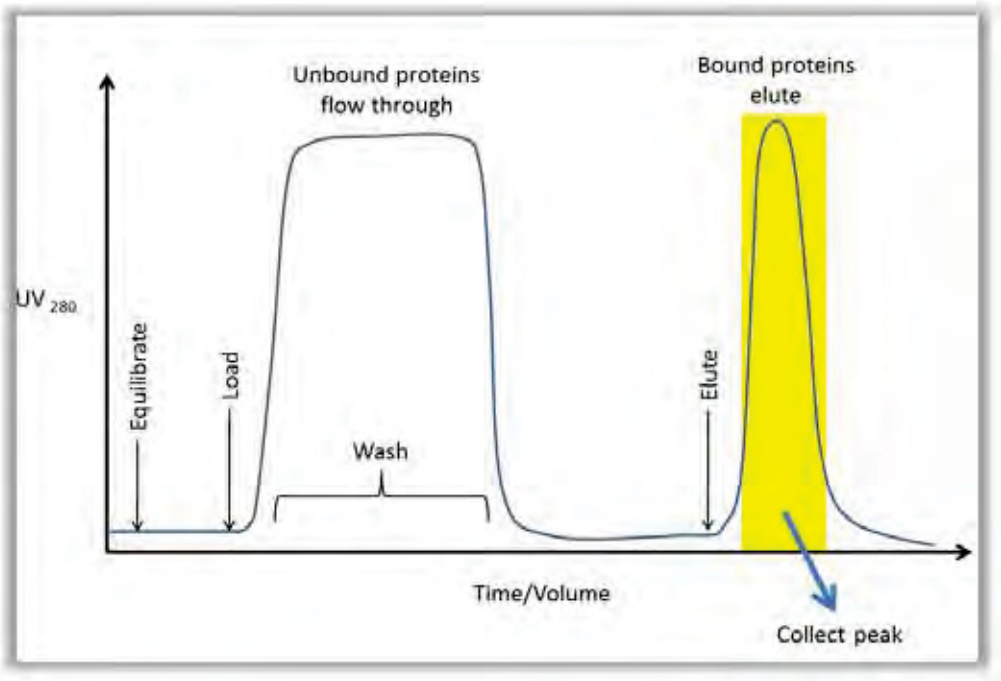
42. There are various types of matrices or resins, which rely on different properties to determine what substances will or will not bind to the matrix. For example, an ion exchange resin is made of either positively-charged or negatively-charged material. When used under the right conditions, the resin will bind to substances of the opposite charge. Thus, a negatively-charged resin (e.g., cation exchange resin) can be used to bind positively-charged substances, and a positively-charged resin (e.g., anion exchange resin) can be used to bind negatively-charged substances.

43. There are different approaches by which a matrix can be used to purify a protein of interest. In one approach, known as "capture" or "bind and elute" purification, the expressed protein of interest binds to the matrix, and the unwanted substances and contaminants stay in the solution that flows over or past the matrix. The protein of interest is thereby "captured" by the matrix, and the remaining solution containing the unwanted substances and contaminants is discarded. Additional solutions can be applied to "wash" the matrix to remove additional unwanted substances and contaminants that do not bind to the matrix. After washing is completed, the conditions in the resin can be changed by applying a different solution (e.g., an elution solution) to release the bound protein of interest from the matrix.

44. Chromatographic separation of proteins can be monitored and displayed visually in a "chromatogram," which is a plot of some measured property of the liquid exiting the

chromatography matrix as a function of time or volume. Measured properties include the degree of absorbance of ultraviolet ("UV") light, e.g., at 280 nm wavelength ("UV_{280}"), which correlates with protein concentration. As the UV meter detects protein in the liquid exiting the column, the UV trace begins to rise as protein concentration increases. The UV trace continues to rise until it peaks or plateaus and subsequently returns to baseline as the protein concentration in the liquid exiting the column decreases. Absorbance at UV_{280} can be plotted on a strip chart or electronic display, generating a graphical representation of the proteins coming off the separation matrix.

45. **Capture Purification.** A graphical representation of a typical chromatography separation run in the "**capture**" mode is illustrated in the Figure below:

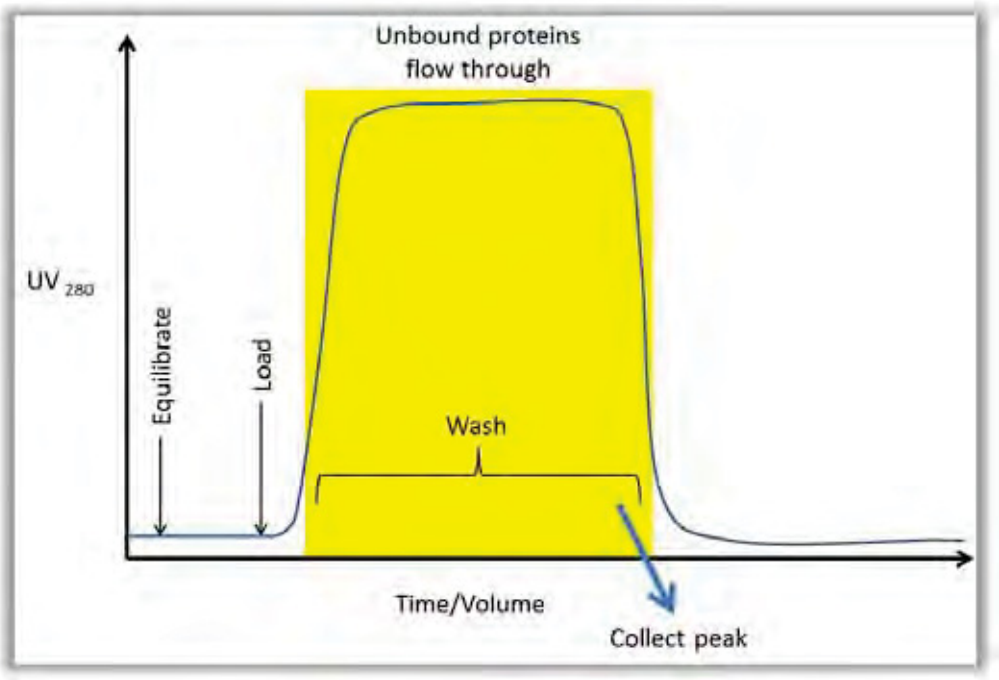


As can be seen in the above figure, a typical chromatogram displays an initial broad peak of proteins that do not bind to the matrix. The column is then washed until this flow-through fraction has completely come off the column, and the UV_{280} reading returns to baseline. Proteins that bind the matrix are then eluted by applying an elution solution to release the bound proteins from the matrix. Chromatography methods are generally optimized to yield sharp, tall elution

peaks that are well separated from other peaks, as in the chromatogram above. This is important because a single, well-resolved elution peak allows a skilled person to monitor the protein to be purified as it elutes from the column and thus collect a more pure sample.

46. **Flow-Through Purification.** In another commonly-used protein separation approach, known as "flow-through" purification, the solution containing the protein of interest is applied to a matrix that binds unwanted substances or contaminants, such as the chemicals that were used to solubilize or refold the protein. The protein of interest does not bind to the matrix, and instead stays in the solution that flows over or past the matrix. This approach is called "flow-through" purification because the protein of interest is recovered in the solution that flows through the resin. In the flow-through approach, the matrix can be washed following the loading step to ensure maximum recovery of the *unbound* protein of interest.[3] In flow-through purification, there is no elution step because the protein of interest does not bind to the matrix but is simply collected in the flow-through / wash fraction, which is further processed to purify the protein of interest. A graphical representation of a typical chromatography separation run in the "**flow-through**" mode is illustrated in the Figure below:

[3] To be clear, **no** person of ordinary skill in the art would consider this an elution step, or some kind of a simultaneous-wash *and* elution step.



VII. THE '997 PATENT.

47. I have reviewed the '997 patent, which is titled "Capture Purification[4] Processes For Proteins Expressed In A Non-Mammalian System." I understand that the '997 patent issued on May 9, 2017. The '997 patent issued from U.S. Application No. 14/599,366 ("the '336 application"), filed on January 16, 2015, which is listed as a divisional of U.S. Application No. 12/822,990 ("the '990 parent application"), filed on June 24, 2010, now the '878 patent. The '997 patent also claims the benefit of priority of U.S. Provisional Application No. 61/220,477, filed on June 25, 2009.[5]

48. I have been asked to assume that June 25, 2009—the date of the earliest filed application on the face of the '997 patent—is the priority date of the '997 patent and to apply that

[4] As I explained in my technological background section above, "capture purification" is a specific type of chromatography that is separate and distinct from "flow through."

[5] At this time, I have not been asked to evaluate whether the '997 patent has made a proper claim of priority to any earlier-filed application(s). I also understand that Mylan has reserved its right to challenge any such claimed priority date(s) for any of the Asserted Claims.

date in forming my analyses and opinions set forth in this declaration.

A. The Asserted Claims of '997 Patent.

49. The '997 patent issued with 30 claims. It is my understanding that Amgen has asserted infringement of only claims 9, 10, 13, 15-20, 21, 24-28, and 29-30 (collectively, "the Asserted Claims") against Mylan. Claim 9, the only asserted independent claim of the '997 patent, reads as follows:

> 9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
> (a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
> (i) a denaturant;
> (ii) a reductant; and
> (iii) a surfactant;
> (b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
> (i) a denaturant;
> (ii) an aggregation suppressor;
> (iii) a protein stabilizer; and
> (iv) a redox component;
> (c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
> (d) washing the separation matrix; and
> (e) eluting the protein from the separation matrix.

('997 patent at col. 22, ll. 36-55).

50. It is my understanding that the disputed claim terms (which I address below) all appear in independent claim 9.

B. The '878 Parent Patent.

51. As I explained above, it is my understanding that the '997 patent is a divisional of the '878 patent, and thus, the '878 patent would be referred to as a "parent" of the '997 "child" patent.

52. I have reviewed the '878 patent and, in my opinion, the specification is identical

in all substantive respects. Additionally, I have reviewed the claims of the '878 patent and compared them to the Asserted Claims of the '997 patent. As I have illustrated in the following table, the '878 patent uses many of the identical claim limitations as the '997 patent:

The '878 Patent	The '997 Patent
7. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising: (a) expressing a protein in a non-native limited solubility form in a non-mammalian cell;	9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
(b) lysing a non-mammalian cell;	[6]
(c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant;	(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant;
(d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component	(b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component
(e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;	(c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
(f) washing the separation matrix; and	(d) washing the separation matrix; and

[6] In my opinion, a person of ordinary skill in the art would know that lysing is an inherent step in the claimed purification process.

The '878 Patent	The '997 Patent
(g) eluting the protein from the separation matrix, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.	(e) eluting the protein from the separation matrix. [7]

53. As illustrated in the above table, in my opinion a person of ordinary skill in the art would conclude that the '878 and '997 patents unquestionably involve substantively the same—if not the *exact* same—subject matter.

C. The Prosecution History of the '997 Patent.

54. I have reviewed the prosecution history of the '997 patent, which, I understand, comprises the prosecution of the '336 application[8] and the '990 parent application[9]. I have considered the prosecution history of the '997 patent in forming my opinions set forth in this declaration. I reserve the right to testify regarding the contents of the prosecution history relevant to the '997 patent as necessary, including based on, or in response to, any submission by Amgen and/or Dr. Willson (and/or any other expert on behalf of Amgen).

[7] It is my understanding that claim 9 of the '997 patent was determined by the Examiner to not be patentably distinct from claim 7 of the '878 patent. (*See* Ex. B, '336 Application Prosecution History ("PH"), 9/1/16 Office Action at 6-7 (MYL(PegF)0146044-45)).

[8] The prosecution history of the '336 application ("'336 Application PH") is located at MYL(PegF)0145383-9670.

[9] The prosecution history of the '990 parent application ("'990 Parent Application PH") is located at MYL(PegF)0149692-50772.

VIII. CLAIM TERMS OF THE '997 PATENT.

A. Undisputed Terms.

1. The preamble and step (a).

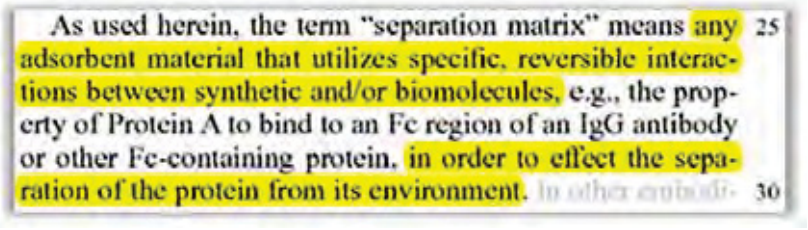
55. I have reviewed the parties' Joint Disputed Claim Terms Chart. (Joint Disputed Claim Terms Chart at 1-17). It is my understanding that the following claim terms / phrases are not disputed:

9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant

56. I agree with the parties that these claim terms/phrases do not require construction. The plain language of each claim term would be well-understood by a person of ordinary skill in the art and is consistent with its plain and ordinary meaning.

2. The "separation matrix."

57. In addition, I understand that the parties reached an agreement that the claim term "separation matrix" should be given its plain and ordinary meaning which is consistent with the definition provided in the '997 patent specification:

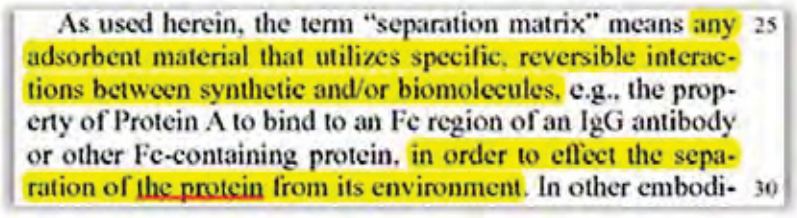

As used herein, the term "separation matrix" means any adsorbent material that utilizes specific, reversible interactions between synthetic and/or biomolecules, e.g., the property of Protein A to bind to an Fc region of an IgG antibody or other Fc-containing protein, in order to effect the separation of the protein from its environment. In other embodi-

('997 patent at col. 7, ll. 25-30 (emphasis added)). Although it is my primary opinion that the

term "separation matrix" does not require construction[10] as the term is sufficiently clear and carries a well-known, plain and ordinary meaning to a person of ordinary skill in the art, I agree that the phrase in the '997 patent specification, "any adsorbent material that utilizes specific, reversible interactions between synthetic and/or biomolecules . . . in order to effect the separation of the protein from its environment," is consistent with that plain and ordinary meaning.

58. Although the parties appear to have reached agreement on this term, I have been asked to explain whether, in my opinion, the agreed-to plain and ordinary meaning (as provided in the '997 patent specification) applies to a particular protein (e.g., the protein of interest or "the expressed protein" to be purified) or extends to just *any* protein as Amgen argues with respect to the "under conditions suitable for the protein to associate with the matrix" claim term (*see* ¶¶ 59-61, 108-125 below).

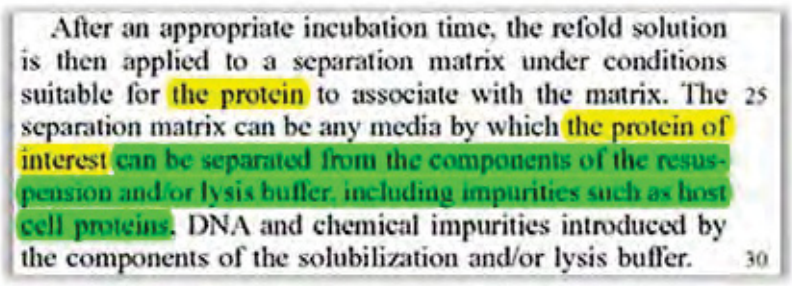
59. In my opinion, the agreed-to plain and ordinary meaning provided in the '997 patent clearly and expressly refers to a specific protein—namely "the [expressed] protein" to be purified (i.e., not just "a protein" or "any protein"):


As used herein, the term "separation matrix" means any adsorbent material that utilizes specific, reversible interactions between synthetic and/or biomolecules, e.g., the property of Protein A to bind to an Fc region of an IgG antibody or other Fc-containing protein, in order to effect the separation of the protein from its environment. In other embodi-

[10] I have reviewed the Order Construing Terms from the related *Amgen v. Sandoz* matter ("*Sandoz* Order"), which involved the '878 patent—parent of the '997 patent, and in my opinion, Amgen previously agreed with my opinion that the term "separation matrix" does not require construction. (Ex. 2, *Sandoz* Order, *Amgen Inc. et al. v. Sandoz Inc. et al.*, No. 14-cv-04741-RS (N.D. Cal. Aug. 4, 2016) (ECF No. 205); *see also* Joint Disputed Claim Terms Chart at 1-8). The '878 patent claims asserted in the *Amgen v. Sandoz* matter contain the identical "separation matrix" claim term that appears in asserted claim 9 of the '997 patent. (*E.g.*, *compare* '878 patent, claim 7, *with* '997 patent, claim 9). In the *Amgen v. Sandoz* matter, Amgen neither proposed a construction nor disputed the plain language of "separation matrix," and thus, the term was not construed.

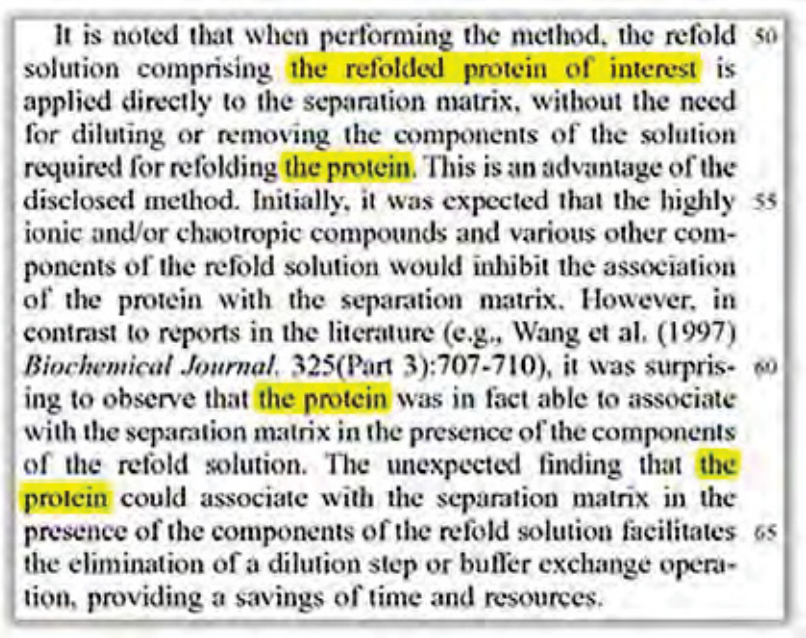
('997 patent at col. 7, ll. 25-37 (emphasis added)). While, at first glance, it may appear to be an inconsequential difference to say "the protein" vs. "a protein", it is my opinion that a strict application of "the protein" (and not "a protein" or "any protein") is germane to the proper understanding of the claim term "separation matrix."

60. First, the entire '997 patent disclosure, including the specification and Asserted Claims, is expressly focused on purifying a very specific protein—namely, "the expressed protein" or, in other words, the protein-of-interest that is to be purified and not just any inconsequential (or incidental) protein that may appear in the process, such as host cell proteins, impurities, etc., which are not the subject of the purification. The following excerpts, for example, reflect this universal purpose of the '997 patent:



After an appropriate incubation time, the refold solution is then applied to a separation matrix under conditions suitable for the protein to associate with the matrix. The separation matrix can be any media by which the protein of interest can be separated from the components of the resuspension and/or lysis buffer, including impurities such as host cell proteins, DNA and chemical impurities introduced by the components of the solubilization and/or lysis buffer.

('997 patent at col. 15, ll. 23-30 (emphasis added)); and



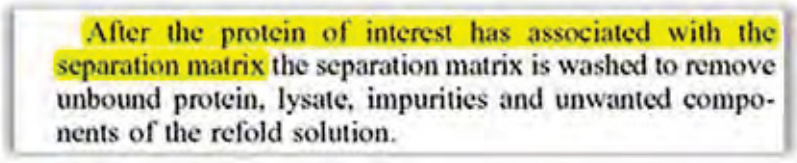
It is noted that when performing the method, the refold solution comprising the refolded protein of interest is applied directly to the separation matrix, without the need for diluting or removing the components of the solution required for refolding the protein. This is an advantage of the disclosed method. Initially, it was expected that the highly ionic and/or chaotropic compounds and various other components of the refold solution would inhibit the association of the protein with the separation matrix. However, in contrast to reports in the literature (e.g., Wang et al. (1997) *Biochemical Journal*. 325(Part 3):707-710), it was surprising to observe that the protein was in fact able to associate with the separation matrix in the presence of the components of the refold solution. The unexpected finding that the protein could associate with the separation matrix in the presence of the components of the refold solution facilitates the elimination of a dilution step or buffer exchange operation, providing a savings of time and resources.

(*id.* at col. 15, ll. 50-67 (emphasis added)). As seen in the above highlights, the "protein of interest" (i.e., the protein to be purified by the claimed method) is the specific protein that is applied to the separation matrix, not just any protein.

61. Second, allowing "the protein" of the agreed-to plain and ordinary meaning to be interpreted as including "a protein" or "any protein" of the non-mammalian expression system[11] would improperly broaden the scope of the Asserted Claims to encompass a *flow-through* method. More specifically, the agreed-to definition requires "separation of **the protein** from its environment"—in other words, the protein to be purified must be separated from solution via binding to the adsorbent material. Yet, if "the protein" in the definition can be just any protein and not specifically the expressed protein to be purified, then the protein of interest will *flow through* and not bind (or even interact) with the adsorbent material of the separation matrix. That method is never considered as part of the '997 patent's claimed invention, which is specifically directed toward "**Capture Purification Processes** For Proteins Expressed In A Non-

[11] In my opinion, this would include thousands of endogenous proteins produced by the host cell.

Mammalian System."[12] Indeed, the protein of interest (i.e., the expressed protein to be purified by the claimed method) is the focus of what must "associate" with the separation matrix under the Asserted Claims:


After the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution.

('997 patent at col. 16, ll. 1-4 (emphasis added)).

B. Disputed Terms

1. *forming a refold solution comprising the solubilization solution and a refold buffer*

Disputed Claim Term or Phrase (in Bold)	**Amgen's Proposal**	**Mylan's Proposal**
(b) **forming a refold solution comprising the solubilization solution and a refold buffer**, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component;	mixing the solution comprising the solubilized protein and one or more of a denaturant, a reductant, and a surfactant with a pH-buffered solution comprising one or more of a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component providing conditions for the protein to refold into its biologically active form	No construction is necessary and that each of the terms should be afforded only their plain and ordinary meaning.

[12] In my opinion, the Court in *Amgen v. Sandoz* ("the *Sandoz* Court") correctly described capture purification as follows: "[C]apture purification utilizes a resin designed to trap protein. The unwanted substances and chemicals stay in the solution and flow over the resin. Scientists discard the solution containing the unwanted contaminants and chemicals, leaving only the resin with the protein to be purified. The process of elation [sic] causes the resin to release the purified protein." (Ex. 2, *Sandoz* Order at 20).

62. I understand that Amgen cited the following intrinsic evidence[13] as support for its proposed construction: the '997 patent at col. 12, ll. 27-32; *id.* at col. 13, l. 65-col. 14, l.3; *id.* at col. 14, ll. 27-40; and *id.* at col. 15, ll. 5-13; Joint Disputed Claim Terms Chart at 2; and also, Amgen's Opening Claim Construction Brief at 3-5, 8-10. For at least the following reasons, I disagree with Amgen's proposed construction and find Amgen's cited intrinsic evidence lacking support for its proposal. In my opinion, the claim term does not require construction. The plain language of the claims represents a plain and ordinary meaning that would be fully understood by a person of ordinary skill in the art, e.g., combining two solutions: a "solubilization solution" and a "refold buffer," both of which are defined in other claim elements.

a. Amgen never proposed a construction in the *Sandoz* litigation.

63. As an initial matter, I have reviewed the Order Construing Claims from the related *Amgen v. Sandoz* litigation (the "*Sandoz* Order"), which involved the '878 patent—parent of the '997 patent—and, it is my opinion that Amgen has taken an inconsistent position with its current proposal for this claim term. (Ex. 2, *Sandoz* Order).[14] As I explained above (*see* ¶¶ 51-52), the '878 parent patent claims asserted in the *Sandoz* litigation contain the identical "forming a refold solution" term that appears in asserted claim 9 of the '997 patent. (*Compare* '878 patent, claim 7 (step (d)), *with* '997 patent, claim 9 (step (b))). However, in the *Sandoz* litigation, Amgen neither proposed a construction nor disputed the plain language of the

[13] I have been informed that so-called "intrinsic evidence" includes the patent itself, including the claims, the specification and, the prosecution history.

[14] I have also reviewed the Willson *Sandoz* Claim Construction Declaration, which Amgen submitted in support of its constructions regarding the '878 patent. Dr. Willson also did not propose a construction for the "forming a refold solution . . . ." claim term and, in my opinion, appeared to rely—as I believe a person of ordinary skill in the art would—on the plain language to form his opinions. As noted above, the Willson *Sandoz* Claim Construction Declaration is filed concurrently herewith as Exhibit 8.

"forming a refold solution" claim term, and thus, the term was not construed.[15]

64. Amgen's position in the *Sandoz* litigation is consistent with my opinion here that the claim term "**forming a refold solution comprising the solubilization solution and a refold buffer**" does not require construction and should be afforded its plain and ordinary meaning as the plain language would be easily and readily understood by a person of ordinary skill in the art.

65. Moreover, as I explain in more detail below, Amgen's current, inconsistent proposal does not reflect the term's plain and ordinary meaning, but instead seeks to read in limitations that do not appear in the claim language or the patent specification.

b. Amgen's proposal includes a construction for an *undisputed* claim term: solubilization solution.

66. As I have noted above (*see* ¶ 55), it is my understanding that the parties have no dispute over the construction for claim 9, step (a), which establishes the "solubilization solution" under the claimed method and reads as follows: "(a) solubilizing the expressed protein in a **solubilization solution** comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant." ('997 patent at col. 22, ll. 39-43 (emphasis added)). Specifically, I understand the parties agreed that step (a), and thus the term "solubilization solution," did not require construction. (Joint Disputed Claim Terms Chart at 1). I agree. In my opinion, neither step (a) nor the term "solubilization solution," as it appears in the Asserted Claims, requires construction.

67. Nevertheless, Amgen's proposal for the "forming a refold solution" claim term

[15] For example, Amgen never asserted in the *Sandoz* litigation that "construction is ***necessary*** because the common usage of the word 'buffer' does not necessarily reflect its use in the '997 Patent" (Amgen Br. at 10 (emphasis added)), even though the term "buffer" is used in ***exactly*** the same way in both the '878 and '997 patents. In my opinion, the plain and ordinary meaning Amgen agreed to in the *Sandoz* litigation should apply here as well.

internally construes the term "solubilization solution" as something other than the plain language appearing in the claims, as I have illustrated in the following table:

Asserted Claim 9, Step (a) (Plain Language)	Amgen's Proposal
"(a) **solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant**."	mixing **the solution comprising the solubilized protein and one or more of a denaturant, a reductant, and a surfactant** with a pH-buffered solution comprising one or more of a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component providing conditions for the protein to refold into its biologically active form

As seen in the above comparison, Amgen attempts to define "solubilization solution" as simply "the solution comprising the solubilized protein and one or more of a denaturant, a reductant, and a surfactant," instead of the undisputed, plain language for the "solubilization solution" from Claim 9, step (a).

68. In my opinion, Amgen's proposal is not consistent with either the parties' agreement or the undisputed, plain language for the "solubilization solution" from Claim 9, step (a). Instead, Amgen is providing a *new* construction. I disagree with Amgen for at least the following reasons:

69. First, Amgen omits "the expressed protein" in favor of the more general, "protein" or "solubilized protein."[16] As I have explained in this declaration (*see* ¶¶ 59-60), the

[16] While this may appear to be a subtle change, Amgen's omission of "the expressed protein" from the plain language of the claims, in my opinion, dramatically alters the scope of the solubilization solution in the claimed method. Under Amgen's construction, the claims are no longer limited to solubilizing (and thus ultimately purifying) the protein-of-interest (i.e., "the expressed protein") that is to be purified. The '997 patent specification confirms that the solubilization solution contains *the* protein, not just any protein: "a refold solution comprising

Asserted Claims use express and clear terms when referring to protein in the claimed method—namely, the expressed protein to be purified.

70. Second, Amgen's proposal does not require using the same "solubilization solution" that is prepared in claim 9, step (a). More specifically, step (a)—which, establishes the "solubilization solution" for the claimed method—requires "***solubilizing*** the expressed protein" in the solution comprising "one or more of" the required components, and, as I explain in more detail below (*see* ¶¶ 75-79), ***that*** step (a) solution is "***the*** solubilization solution" used in step (b). In other words, the solution "in" which the expressed protein was solubilized is "the solubilization solution." By comparison, Amgen's proposal only requires "solubilized protein" (i.e., *any* protein) in a solution (i.e., *any* solution, not necessarily the solution that the expressed protein was solubilized in) with "one or more of" the listed components (i.e., *any* components). Amgen's proposal thus allows for the "solubilization solution" to be newly-defined in **step (b)** without any connection to the "solubilization solution" from **step (a)**—an interpretation that I strongly disagree with.

71. As I stated above (*see* ¶ 36) I have also been informed that claim terms are presumed to be used consistently throughout a patent and additionally presumed to carry the same construed meaning in the same patent or related patents. I agree that a person of ordinary skill in the art would expect the same term to have the same meaning throughout a patent specification and claims. Amgen's proposals here, however, clearly do not keep with that practice. In my opinion, Amgen is proposing separate and inconsistent constructions for the claim term "solubilization solution" which appears in both the undisputed, **step (a)** claim term

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the solubilization solution ***(which comprises <u>the</u> protein)***, and a refold buffer is formed." ('997 patent at col. 14, ll. 27-29 (emphasis added)).

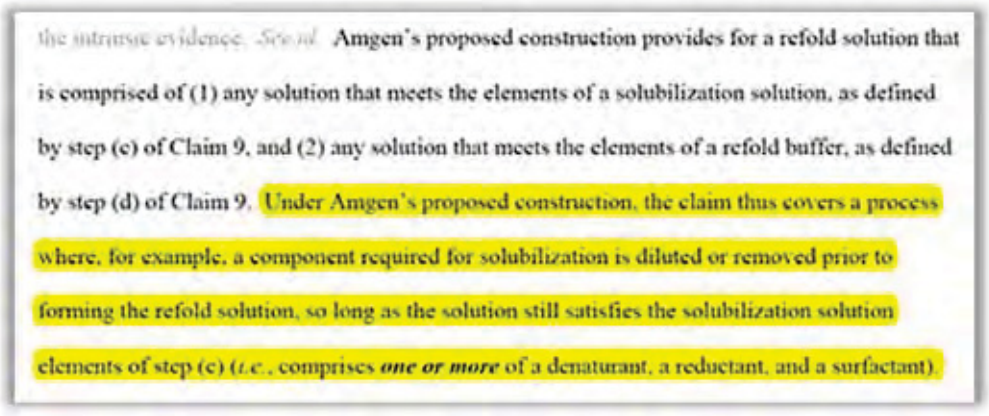
and the disputed "forming a refold solution" (**step (b)**) claim term.

72. For at least these reasons, I disagree with Amgen's proposed construction for the claim term "forming a refold solution comprising the solubilization solution and a refold buffer."

c. Amgen's position regarding the "one or more of" claim language is directly contradicted by prior arguments in this case.

73. I have been asked to review arguments Amgen made in attempting to distinguish prior art to the '997 patent and evaluate whether those arguments are consistent with Amgen's current proposed construction for the "forming a refold solution" claim term. As I explain in the following paragraphs, in my opinion, Amgen has taken inconsistent positions and, indeed, Amgen's arguments asserting validity of the '997 patent directly contradict its current proposal.

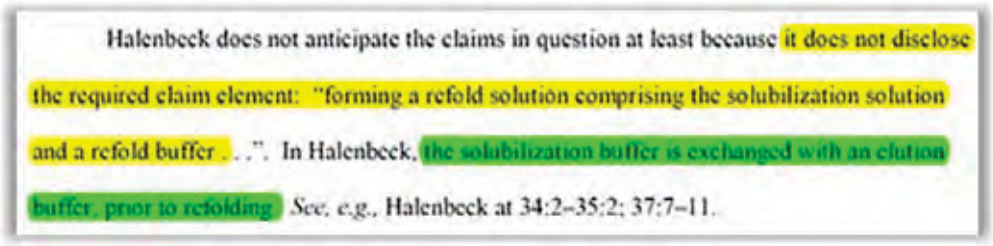
74. Amgen makes the following argument in support of its current, proposed construction for the "forming a refold solution" claim term:


the intrinsic evidence. *See id.* **Amgen's proposed construction provides for a refold solution that is comprised of (1) any solution that meets the elements of a solubilization solution, as defined by step (c) of Claim 9, and (2) any solution that meets the elements of a refold buffer, as defined by step (d) of Claim 9. Under Amgen's proposed construction, the claim thus covers a process where, for example, a component required for solubilization is diluted or removed prior to forming the refold solution, so long as the solution still satisfies the solubilization solution elements of step (c) (*i.e.*, comprises *one or more* of a denaturant, a reductant, and a surfactant).**

(Amgen Br. at 8-10 (emphasis added); *id.* at 9 ("The claim itself is thus silent as to whether any components utilized for solubilization can be removed before forming the refold solution . . . . As long as one or more of the listed components remain, the solubilization solution remains a solubilization solution."). In other words, Amgen argues that the "solubilization solution" in **step (b)** is met so long as "one of more of" the itemized components (i.e., a denaturant, a

reductant, and a surfactant) are present ***even if*** one (or more) of the elements that made up the original, **step (a)** "solubilization solution" is ***"diluted or removed"*** before it is combined with the refold buffer to form a refold solution.[17]

75. Yet, in my opinion, Amgen took the opposite position to distinguish prior art and argue validity of the parent '878 patent.[18] For example, in the *Sandoz* litigation, Amgen distinguished Halenbeck[19] by arguing:


Halenbeck does not anticipate the claims in question at least because it does not disclose the required claim element: "forming a refold solution comprising the solubilization solution and a refold buffer . . .". In Halenbeck, the solubilization buffer is exchanged with an elution buffer, prior to refolding. *See, e.g.*, Halenbeck at 34:2–35:2; 37:7–11.

(Ex. 10, Amgen Statement Under 42 U.S.C. § 262(*l*)(3)(C) against Sandoz at 17, *Amgen Inc. et al. v. Sandoz Inc. et al.*, No. 16-cv-01276-SRC-CLW (D.N.J. May 3, 2016) (ECF No. 28-5) (emphasis added)). Amgen made a similar argument when responding to Mylan's invalidity argument concerning Halenbeck. (Amgen Statement Under 42 U.S.C. § 262(*l*)(3)(C) against Mylan at 24). What Amgen refers to in Halenbeck as "an elution buffer" comprises 4 M Urea **(a**

[17] I disagree with Amgen's position that one or more components can be removed from the original "solubilization solution" of **step (a)** and somehow meet "the solubilization solution" of **step (b)**. As I explain in more detail below (*see* ¶¶ 76-79), it is my opinion that "***the*** solubilization solution" of **step (b)** must be the same solution as in **step (a)**. Moreover, the patent specification provides no guidance or disclosure regarding diluting or removing components of the "solubilization solution" nor does it explain what might happen to the solubilized protein if one or more of the components used to solubilize the protein were diluted or removed.

[18] The '878 patent contains the exact same "forming a refold solution" limitation as the '997 patent.

[19] "Halenbeck" refers to International Patent Application Publication No. WO 1988/08003 to R.F. Halenbeck et al. (October 20, 1988). Halenbeck is filed concurrently herewith as Exhibit 9.

denaturant)[20], 0.1 M Tris, 5 mM EDTA and 2 mM DTT **(a reductant)**[21]—in other words, the "purified solution" in Halenbeck "comprises ***one or more*** of a denaturant, a reductant, and a surfactant."[22]

76. In my opinion, if Amgen's current proposal—i.e., "[a]s long as one or more of the listed components remain, the solubilization solution remains a solubilization solution"—is applied to Halenbeck, a person of ordinary skill in the art would easily conclude that the "purified solution" in Halenbeck "comprises ***one or more*** of a denaturant, a reductant, and a surfactant," and therefore qualifies as a "solubilization solution" under the Asserted Claims—directly contradicting Amgen's prior argument regarding Halenbeck.

d. Amgen's proposal is contradicted by the plain language of the Asserted Claims.

77. For the following reasons, I disagree with Amgen's arguments that **(i)** the Asserted Claims are "silent as to whether any components utilized for solubilization can be [diluted or] removed before forming the refold solution" and **(ii)** "[a]s long as one or more of the listed components remain, the solubilization solution remains a solubilization solution."

78. First, in my opinion, the claims are <u>not</u> "silent" with respect to "whether any components utilized for solubilization [in **step (a)**] can be [diluted or] removed before forming

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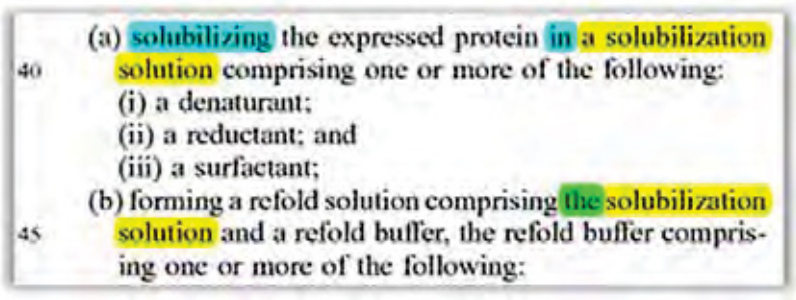
[20] *See* '997 patent at col. 2, ll. 43-45.

[21] *See* '997 patent at col. 2, ll. 45-47.

[22] To clarify, the process disclosed in Halenbeck involves: **(1)** solubilizing the protein to be purified in a solubilization solution that is "adjusted to 1 liter 8 M urea, 2 mM DTT, 5 mM EDTA and 20 mM Tris, pH 8.5" (*see* Ex. 9, Halenbeck at 34, ll. 18-26), followed by **(2)** partially purifying the solubilization solution to a final solution of the protein to be purified comprising "4 M urea, 0.1 M Tris, pH 8.5, 5 mM EDTA, and 2 mM DTT" (*see id.* at 34, l. 27-35, l. 2), diluting the concentration of urea from 8 M to 4 M. To use Amgen's language, "one or more of the listed components [urea (a denaturant) and DTT (a reductant)] ***remain***," and therefore, "the solubilization solution remains a solubilization solution."

the refold solution [in **step (b)**]." Instead, in my opinion, the plain language of the claims speaks quite clearly on this point:


(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
(i) a denaturant;
(ii) a reductant; and
(iii) a surfactant;
(b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:

('997 patent col. 22, ll. 39-50 (emphasis added)). As I have illustrated in the above highlighted excerpt of Claim 9, **step (a)** informs a person of ordinary skill in the art how to make "the solubilization solution" under the claimed method: (i) solubilizing the expressed protein in (ii) a solubilization solution comprising one or more of the listed components. The subsequent reference to "solubilization solution" in the claimed method—**step (b)**—is preceded by a definite article, "the"—i.e., "**the** solubilization solution." In my opinion, a person of ordinary skill in the art would read "**the** solubilization solution" in **step (b)** as expressly referring back to the "solubilization solution" made in **step (a)**—more specifically, the solution "in" which the expressed protein was solubilized. In other words, if something is "diluted or removed" from the "solubilization solution" made in **step (a)**, then the resulting solution is no longer the solution that the expressed protein was "*solubilize[ed] . . . in*,"[23] and therefore, in my opinion, is no longer "the solubilization solution" of the claimed method.

79. In contrast, I understand Amgen's argument to allow for the "solubilization

[23] In my opinion, this is particularly true for solutions with multiple components because a person of ordinary skill in the art would understand that each separate component may contribute (to some degree) to "***solubilizing*** the expressed protein ***in*** a solubilization solution." Thus, in my opinion, to be "the solubilization solution" that the expressed protein was solubilized in, one cannot "dilute or remove" components that contributed to "solubilizing" the expressed protein.

solution" of **step (a)** to be defined by the presence of just "one" of the listed components ***even if*** "more" of the listed components are present. However, in my opinion, that is not consistent with the Asserted Claims' use of the phrase "one or more." A person of ordinary skill in the art would understand that if the "solubilization solution" in **step (a)** contains just "one" of the listed components (e.g., one denaturant), then that is "**the** solubilization solution" for the subsequent steps; whereas, if the "solubilization solution" in **step (a)** contains "more" of the listed components (e.g., one denaturant and one reductant), then *that* solution (e.g., with both) is "**the** solubilization solution" for the subsequent steps. This is particularly important for solutions with multiple components because a person of ordinary skill in the art would understand that each separate component may contribute (to some degree) to "***solubilizing*** the expressed protein ***in*** a solubilization solution."

80. I have prepared the following table in attempt to illustrate the overbreadth of Amgen's proposal:

		Person of Ordinary Skill in the Art	**Amgen**
	Step (a): "solubilization solution" comprises solubilized, expressed protein +___:	Step (b): "**the** solubilization solution" comprises solubilized, expressed protein +___	Step (b): "the solubilization solution" comprises solubilized, expressed protein +___
1.	D, R, and S	*Same as Step (a):* D, R, and S	*Any amounts of:* D, R, and S D and R D and S R and S D R S
2.	D and R	*Same as Step (a):* D and R	*Any amounts of:* D, R, and S D and R D and S R and S D R S
3.	D and S	*Same as Step (a):* D and S	*Any amounts of:* D, R, and S D and R D and S R and S D R S
4.	R and S	*Same as Step (a):* R and S	*Any amounts of:* D, R, and S D and R D and S R and S D R S

5.	D	*Same as Step (a):* D	*Any amounts of:* D, R, and S D and R D and S R and S D R S
6.	R	*Same as Step (a):* R	*Any amounts of:* D, R, and S D and R D and S R and S D R S
7.	S	*Same as Step (a):* S	*Any amounts of:* D, R, and S D and R D and S R and S D R S

As I have shown in the above table, a person of ordinary skill in the art would understand the plain language of **step (b)** to require the same "solubilization solution" (i.e., none of the listed components removed or diluted). Whereas, under Amgen's proposal, one could define "the solubilization solution" of **step (b)** in a nearly infinite number of ways because any (or all) of the components from the "solubilization solution" of **step (a)** can be "diluted or removed" so long as some, undefined amount of just one "remains." I refuse to believe that the named inventors intended such ambiguity in the claims, just as I refuse to believe that a person of ordinary skill in the art would reach Amgen's understanding of "the solubilization solution" in **step (b)**.[24]

[24] I must further point out that Amgen expressly does not limit "the solubilization solution" of **step (b)** to the same denaturant (D), reductant (R) and/or surfactant (S) components as used in

81. I also disagree with Amgen's reliance on the '997 patent specification to support its proposal that a diluted version of the **step (a)** "solubilization solution" is contemplated as "the solubilization solution" of **step (b)**:

> solubilization solution remains a solubilization solution. The specification of the '997 Patent also teaches that components utilized for solubilization must at least be diluted to form the refold solution. (*See* Dkt. No. 101-1, '997 Patent, at col. 19:25-27, 20:48-50 (Examples 1 and 2 both teach that a solubilization solution "was diluted" into a refold buffer for refolding.)) Amgen's

(Amgen Br. at 10). The *dilution* Amgen is referring to in Examples 1 and 2 is quite simply **step (b)** of the claimed method—in other words, combining "the solubilization solution" of **step (a)** with a "refold buffer." This disclosure does not support Amgen's argument that "the solubilization solution" of **step (b)** can differ—via, e.g., dilution or removal of solubilizing components—from the solubilization solution that is made in **step (a)**.[25]

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step (a): "Under Amgen's proposed construction, the claim thus covers a process where, ***for example***, a component required for solubilization is diluted or removed prior to forming the refold solution, so long as the solution still satisfies the solubilization solution elements of step (c) [sic] (i.e., comprises one or more of a denaturant, a reductant, and a surfactant)." (Amgen Br. at 8 (emphasis added)). I understand Amgen's proposal to therefore allow the D, R and/or S in **step (a)** be replaced entirely with a different D, R, and/or S component. For example, applying Amgen's proposal, the "solubilization solution" made in accordance with **step (a)** may comprise only D1, but "the solubilization solution" of **step (b)** may remove D1 entirely and replace it with D2. (*See, e.g.*, *id.*). I strongly disagree with this overly-broad interpretation of the claim language.

[25] In the event Amgen or Dr. Willson attempt to argue that the filtration step in Examples 1 and 2 somehow contradict my opinion here, I disagree. While filtration may remove suspended particles, those are not soluble and thus are not part of the "solution;" therefore, in my opinion, filtering the solubilization solution made in **step (a)** would not alter or change the concentration or composition of the soluble D, R, and/or S components in the way Amgen is proposing with its "dilute or remove" argument.

e. Amgen's proposal also reads in "a pH-buffered solution"—a functional limitation from the specification that does not appear in the claims.

82. As I stated above (*see* ¶ 32), it is my understanding that claim construction begins with the claim language and, in general, claims are construed to have their plain and ordinary meaning as understood by a person of ordinary skill in the art.

83. In contrast, I understand Amgen and Dr. Willson to be arguing that the '997 patent claims require something *other than* the plain and ordinary meaning of the term "buffer." (*See* Amgen Br. at 10 ("Amgen's proposed construction is necessary because common usage of the word 'buffer' ***does not necessarily reflect its use in the '997 Patent***.") (emphasis added); Willson Decl. ¶ 44). To that end, Amgen's proposed construction for the "forming a refold solution" claim term reads in the phrase, "a pH-buffered solution," which, in my opinion, represents a functional limitation taken out of context from the specification.

84. For at least the following reasons, which I provide in more detail below, I disagree with Amgen's proposed, added limitation: **(i)** the claim language is sufficiently clear and consistent with the plain and ordinary meaning of "buffer"; **(ii)** the named inventors did not define "buffer" in a way that is not consistent with its plain and ordinary meaning; **(iii)** nothing in the patent specification warrants reading Amgen's "pH-buffered solution" limitation into the claims; and **(iv)** the specification expressly contradicts reading in such a limitation.

(i) *The claim language is sufficiently clear and is consistent with the plain and ordinary meaning of "buffer."*

85. There is nothing unclear about the meaning of "buffer" as it appears in the "forming a refold solution" claim term to a person of ordinary skill in the art. The word "buffer" is a *very* well-known, well-understood term in the art of protein purification and, in my opinion, is used in **step (b)** exactly how a person of ordinary skill in the art would use and understand it.

Accordingly, in my opinion, the term "buffer" does not require construction and would be fully understood by a person of ordinary skill in the art.

(ii) *The named inventors did not define buffer.*

86. As I stated above, it is my understanding that one exception to the general rule of applying a claim term's plain and ordinary meaning is when the inventors have defined terms in the specification in a way that is not consistent with the plain and ordinary meaning of the term.[26] In my opinion, this exception does not apply to the '997 patent.

87. Amgen cites the following as apparent support for its argument that "[t]he specification of the '997 Patent teaches that 'buffer' has a particular meaning in this field of art, namely that 'the buffer component of the refold solution is to maintain the pH of the refold solution'":

> The function of the buffer component of the refold solution is to maintain the pH of the refold solution and can comprise any buffer that buffers in the appropriate pH range. Examples of the buffering component of a refold buffer that can be employed in the method include, but are not limited to, phosphate buffers, citrate buffers, tris buffer, glycine buffer, CHAPS, CHES, and arginine-based buffers, typically at levels of 5-100 mM (e.g., 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75 80, 85, 90, 95 or 100, mM).

('997 patent at col. 15, ll. 5-13; *see also* Joint Disputed Claim Terms Chart at 2, Amgen Br. at 10 ("The specification of the '997 Patent teaches that 'buffer' has a particular meaning in this field of art, namely that 'the buffer component of the refold solution is to maintain the pH of the refold solution.'" (citing '997 patent at col. 15, ll. 5-8)). Amgen also argues that its proposed construction "is necessary because common usage of the word 'buffer' ***does not necessarily***

[26] Amgen does not appear to argue that the second exception—when the patentee excludes, restricts or otherwise disavows the full scope of a claim term either in the specification or during prosecution—applies to the "buffer" of the claimed method.

reflect its use in the '997 Patent." (Amgen Br. at 10 (emphasis added)).[27] I disagree.

88. First, the paragraph Amgen relies upon expressly refers to "the ***buffer component*** of the refold solution." ('997 patent at col. 15, ll. 5-13 (emphasis added)). As I have illustrated in the following table, a "buffer component" is not an itemized requirement of either the "solubilization solution" or the "refold buffer" (which, together, form the refold solution) under the Asserted Claims:

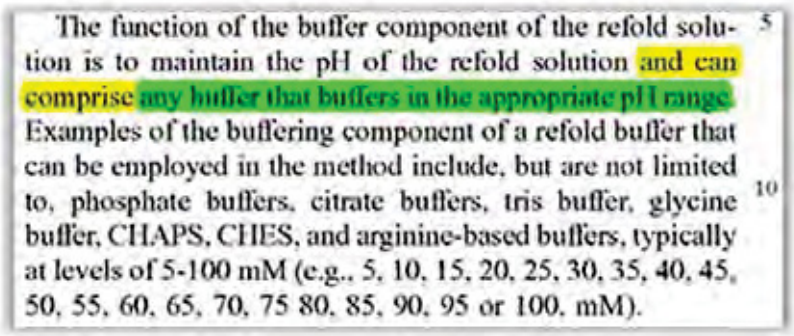
"solubilization solution"	"refold buffer"
(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant;	(b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component;

(*Id.* at col. 22, ll. 39-50 (claim 9) (emphasis added)).[28] Accordingly, in my opinion, there is no basis to import a functional limitation of something that is not even required in the "refold solution" of the Asserted Claims.

89. Second, the paragraph expressly uses optional language (e.g., "***can*** comprise") for the "buffer[ing] in the appropriate pH range" limitation that Amgen seeks to read into the claims:

[27] I understand Amgen's argument here as suggesting that the named inventors of the '997 patent provided a definition of "buffer" that differs from the term's plain and ordinary meaning (i.e., common usage). I disagree (*see* ¶¶ 83-90).

[28] I must also note that the '997 patent specification provides express definitions for each of the listed components: "denaturant" (*see* col. 5, ll. 35-44), "reductant" (*see* col. 14, ll. 10-16), "surfactant" (*see* col. 14, ll. 17-22), "aggregation suppressor" (*see* col. 5, ll. 45-53), "protein stabilizer" (*see* col. 5, ll. 54-63), and "redox component" (*see* col. 4, ll. 50-51).

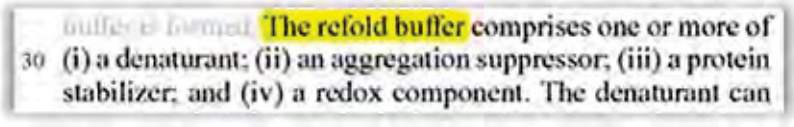


The function of the buffer component of the refold solution is to maintain the pH of the refold solution and can comprise any buffer that buffers in the appropriate pH range. Examples of the buffering component of a refold buffer that can be employed in the method include, but are not limited to, phosphate buffers, citrate buffers, tris buffer, glycine buffer, CHAPS, CHES, and arginine-based buffers, typically at levels of 5-100 mM (e.g., 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75 80, 85, 90, 95 or 100, mM).

('997 patent at col. 15, ll. 5-13 (emphasis added)). In my opinion, this further tells a person of ordinary skill in the art that the functional, pH-buffering aspect of the "buffer component" (which, as I note above is not even a listed component of the Asserted Claims) is not a required element of the "refold solution."

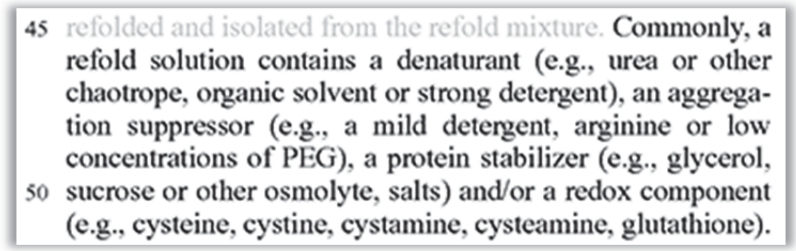
(iii) ***The '997 patent specification contradicts reading in the "pH-buffered solution" limitation.***

90. The '997 patent specification repeatedly (and consistently) describes the composition of the "refold buffer" using the same language as appears in the Asserted Claims (i.e., without listing a "buffer component" as a required item):



buffer is formed. The refold buffer comprises one or more of (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component. The denaturant can

('997 patent at col. 14, ll. 29-31 (emphasis added); *id.* at col. 2, ll. 30-33 (same)). The '997 patent specification further describes the common composition of a "refold solution" without mention of a "buffer component" or the functional aspect of a "buffer component":



refolded and isolated from the refold mixture. Commonly, a refold solution contains a denaturant (e.g., urea or other chaotrope, organic solvent or strong detergent), an aggregation suppressor (e.g., a mild detergent, arginine or low concentrations of PEG), a protein stabilizer (e.g., glycerol, sucrose or other osmolyte, salts) and/or a redox component (e.g., cysteine, cystine, cystamine, cysteamine, glutathione).

(*Id.* at col. 4, ll. 45-51). These consistent descriptions of what constitutes a "refold buffer" or "refold solution" within the '997 patent confirm my opinion that the "pH buffered solution" limitation should not be read into the claims.

* * *

91. For these additional reasons, I disagree with Amgen's proposed construction for the claim term "forming a refold solution comprising the solubilization solution and a refold buffer."

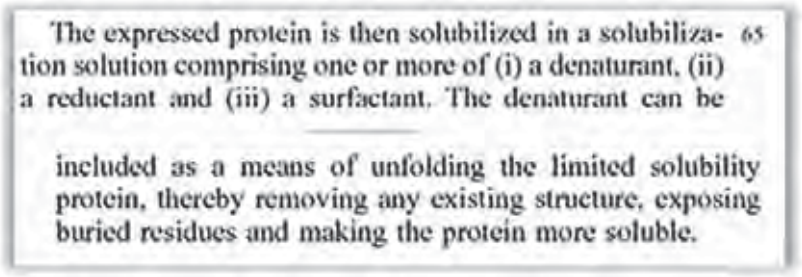
f. Amgen's proposal also reads in "providing conditions for the protein to refold into its biologically active form"—another functional limitation that does not appear in the claims.

92. I also disagree with Amgen's proposed construction because it reads in a second functional limitation from the specification that, in my opinion, a person of ordinary skill in the art would not recognize in the plain language of the claims. Specifically, Amgen seeks to limit the refold solution to one "providing conditions for the protein to refold into its biologically active form." Although neither Amgen nor Dr. Willson presents an explanation for this limitation in Amgen's opening papers,[29] Amgen's apparent support for reading that limitation into the claims are the following excerpts from the '997 patent specification:

such as inclusion bodies. These aggregates comprise protein that is typically not biologically active or less active than the completely folded native form of the protein. In order to
30 produce a functional protein, these inclusion bodies often need to be carefully denatured so that the protein of interest can be extracted and refolded into a biologically active form.

('997 patent at col. 12, ll. 27-32 (emphasis added)); and

[29] I reserve the right to submit a reply in the event Amgen and/or Dr. Willson submit any evidence or argument on this topic in their next submissions.



The expressed protein is then solubilized in a solubilization solution comprising one or more of (i) a denaturant, (ii) a reductant and (iii) a surfactant. The denaturant can be

included as a means of unfolding the limited solubility protein, thereby removing any existing structure, exposing buried residues and making the protein more soluble.

(*id.* at col. 13, l. 65-col. 14, l. 3). (*See* Joint Disputed Claim Terms Chart at 1-2). As I explain in the following paragraphs, neither the above disclosures nor any other portion of the '997 patent specification support reading such a limitation into the claims.

93. First, in my opinion, nothing in the Asserted Claims require either **(i)** that the protein actually refolds in the refold solution (e.g., the protein may refold upon binding to the separation matrix and/or during or after elution and/or not at all) as Amgen's proposed, added limitation suggests; or **(ii)** that the claimed method result in a "biologically active form" of the expressed protein. Instead, in my opinion, a person of ordinary skill in the art would interpret the Asserted Claims as reading much more broadly—specifically, so long as the "refold solution" comprises the required components of the claims (i.e., **the** solubilization solution of step (a) and a refold buffer comprising one or more of (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component) then it is irrelevant under the Asserted Claims whether the protein to be purified actually refolds during that step or whether the refold solution actually "provid[es] conditions for the [expressed] protein to refold into its biologically active form." In other words, in my opinion, a person of ordinary skill in the art would recognize that there are no functional limitations on the "refold solution" in any of the Asserted Claims.

94. Second, in my opinion, a person of ordinary skill in the art would know that not all proteins falling within the scope of the claimed method need to be refolded. Although the Examples of the '997 patent illustrate purification of so-called "complex proteins," independent

claim 9 and several other dependent claims are clearly drafted much more broadly to encompass much simpler proteins that may not require refolding. (*E.g.*, *Compare* Claim 9 ("purifying ***a*** protein expressed"), *with* Claim 11 ("wherein the protein is a complex protein") *and* Claim 12 ("wherein the complex protein is selected from the group consisting of a multimeric protein, an antibody, a peptibody, and an Fc fusion protein.")). The specification confirms that the claimed method was not intended for only complex proteins and may cover purification of much simpler proteins that do not require refolding: "The protein ***can be*** a complex protein . . . ." ('997 patent at col. 2, ll. 39-42 (emphasis added)). Therefore, in my opinion, a person of ordinary skill in the art would not limit the broad language of claim 9 to "providing conditions for the protein to refold into its biologically active form" because, among other things, that limitation would not necessarily apply to the full scope of proteins covered under the claimed method.

95. Third, the '997 patent specification discloses that some proteins falling within the scope of the claimed purification method actually require "further" refolding after being eluted from the separation matrix:

> In some situations, the protein can then be further purified from the elution pool and can be further refolded, if necessary. In other situations the protein need not be further purified and instead can be further refolded directly in the elution pool, if necessary.

('997 patent at col. 16, ll. 36-40 (emphasis added)). Accordingly, in my opinion, adding Amgen's proposed "providing conditions for the protein to refold into its biologically active form" limitation would exclude embodiments of the claimed method wherein the protein to be purified requires "further" refolding *after* eluting to achieve its biologically active form.

96. Fourth, claim 9 is not limited with respect to the type of chromatography that may

be used,[30] and therefore, in my opinion, would be understood by a person of ordinary skill in the art to include, e.g., affinity chromatography. It is well-known to a person of ordinary skill in the art that affinity chromatography does not require the protein to be in its biologically active form to bind to the matrix. For example, immobilized metal affinity chromatography (IMAC) is a specialized variant of affinity chromatography where proteins are separated according to their affinity for certain metal ions that have been immobilized onto an insoluble matrix.

* * *

97. For these additional reasons, I disagree with Amgen's proposed construction for the claim term "forming a refold solution comprising the solubilization solution and a refold buffer." As I have explained above, a person of ordinary skill in the art would understand the plain language of this term to mean exactly what it says, "**forming a refold solution comprising the solubilization solution and a refold buffer;**" and, a person of ordinary skill in the art would further understand that "the solubilization solution" is the same solubilization solution made in step (a) of the claimed method. Accordingly, in my opinion, the claim term does not require construction.

[30] By comparison, the '878 patent expressly excludes affinity chromatography: "wherein the separation matrix is a non-affinity resin . . . ." ('878 patent at col. 22, ll. 3-28 (claim 7)).

2. *applying the refold solution to a separation matrix*

Disputed Claim Term or Phrase (in Bold)	Amgen's Proposal	Mylan's Proposal
(c) **applying the refold solution to a separation matrix** under conditions suitable for the protein to associate with the matrix	applying the refold solution to a column that contains the separation matrix without intervening steps of dilution, centrifugation, dialysis, or precipitation	"applying the refold solution to a separation matrix without removing components of or diluting the refold solution" Ex. 2, *Sandoz* Order at 20-25

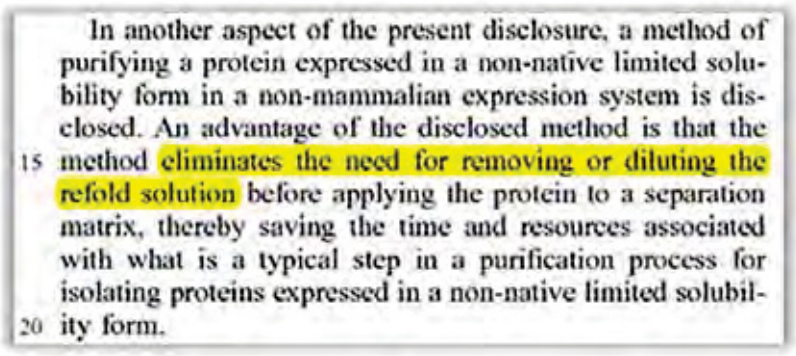
98. For the following reasons, I disagree with Amgen's proposal. In my opinion, the claim term should be construed in accordance with its plain and ordinary meaning as "applying the refold solution to a separation matrix without removing components of or diluting the refold solution."

a. **The plain and ordinary meaning of "applying the refold solution to a separation matrix" is well-understood to a person of ordinary skill in the art.**

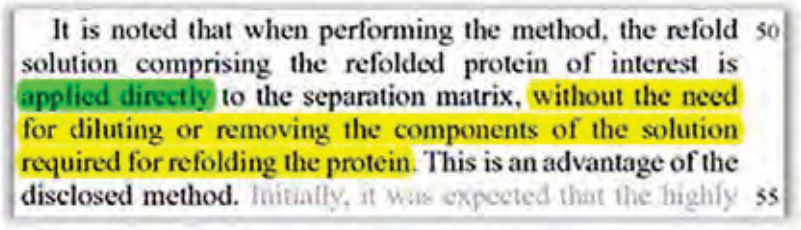
99. In my opinion, there is nothing unclear about the meaning of "applying" as it appears in the disputed "applying the refold solution to a separation matrix" claim term to a person of ordinary skill in the art. Indeed, applying a solution to a separation matrix is a *very* well-known, well-understood, and frequently-practiced procedure in the art of protein purification. In my opinion, claim 9, **step (c)** uses this phrase—"applying the [] solution to a separation matrix"—exactly how a person of ordinary skill in the art would use and understand it. This is elementary to a person of ordinary skill in the art of protein purification and, in my opinion, nothing in the claim language demands construction for it to be understood. Accordingly, in my opinion, the term should be afforded its plain and ordinary meaning as "applying the refold solution to a separation matrix without removing components of or diluting the refold solution."

b. The '997 patent specification and prosecution history confirm my opinion that the term be construed as "applying the refold solution to a separation matrix without removing components of or diluting the refold solution."

100. The specification expressly discloses that "applying" the refold solution under the Asserted Claims is achieved without "removing or diluting the refold solution"—i.e., Mylan's proposal:


In another aspect of the present disclosure, a method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system is disclosed. An advantage of the disclosed method is that the method eliminates the need for removing or diluting the refold solution before applying the protein to a separation matrix, thereby saving the time and resources associated with what is a typical step in a purification process for isolating proteins expressed in a non-native limited solubility form.

('997 patent at col. 12, ll. 11-20 (emphasis added); *id.* at col. 12, ll. 38-50). Moreover, the '997 patent specification describes "directly applying" exactly the same way:


It is noted that when performing the method, the refold solution comprising the refolded protein of interest is applied directly to the separation matrix, without the need for diluting or removing the components of the solution required for refolding the protein. This is an advantage of the disclosed method. Initially, it was expected that the highly

(*Id.* at col. 15, ll. 50-55 (emphasis added)). Accordingly, in my opinion, a person of ordinary skill in the art would understand that there is no substantive difference between "applying" or "directly applying" within the context of the '997 patent. I therefore disagree with Amgen's argument that "applying" (in the '997 patent) requires a different construction than "directly applying" (in the '878 patent)—in my opinion, as confirmed by the patent specification, a person of ordinary skill in the art would expect these to mean the same thing.

101. In fact, Amgen's statements during prosecution further confirm my opinion. In

response to a rejection of a claim that included the *identical* limitation, Amgen told the Examiner that "applying the refold solution" equated to "the ***direct application*** of refold solution to the separation matrix." ('990 Parent Application PH, 1/25/2013 Response at 7-8 (MYL(PegF)0150160-61) (emphasis added)). In my opinion, Amgen's statement to the Examiner made clear that the step of "applying the refold solution to a separation matrix" was fully intended to be synonymous with "directly applying" the refold solution to the separation matrix. Indeed, the Examiner implicitly recognized the existence of the "directly applying" element in the application leading to the '997 patent. (Ex. B, '336 Application PH, 9/1/2016 Office Action at 6-7 (MYL(PegF)0146044-45); Ex. C, '336 Application PH, 2/21/2017 Terminal Disclaimer (MYL(PegF)0149596)). Therefore, in my opinion, "applying the refold solution to a separation matrix" should be construed consistent with the *Sandoz* Court's construction for "directly applying the refold solution to a separation matrix," which I agree with and further understand Amgen has not disputed.[31]

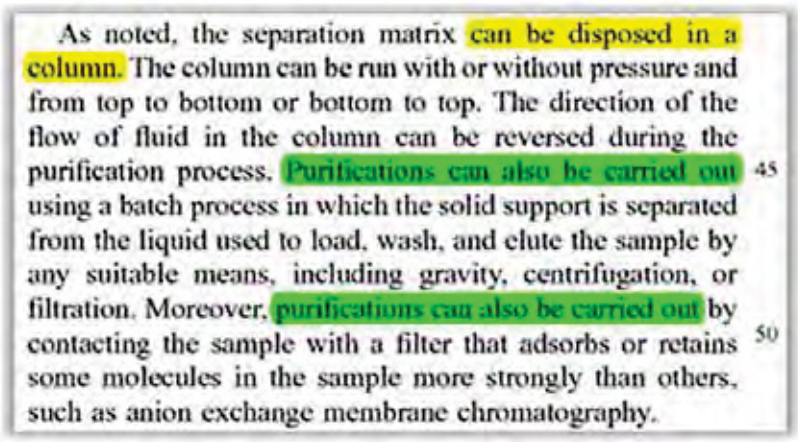
c. Amgen's proposal reads in "a column that contains the separation matrix"—a limitation from a single embodiment that appears nowhere in the claims.

102. As an initial matter, neither Amgen nor Dr. Willson provides an explanation or any evidence supporting their added limitation of "a column that contains the separation matrix." Accordingly, I expressly reserve the right to submit a reply in the event Amgen or Dr. Willson submits any evidence or argument in their next submissions.

103. I disagree with Amgen's proposal for at least the following reasons. First, nothing in the plain language of the claims would inform a person of ordinary skill in the art that the Asserted Claims are limited to column chromatography.

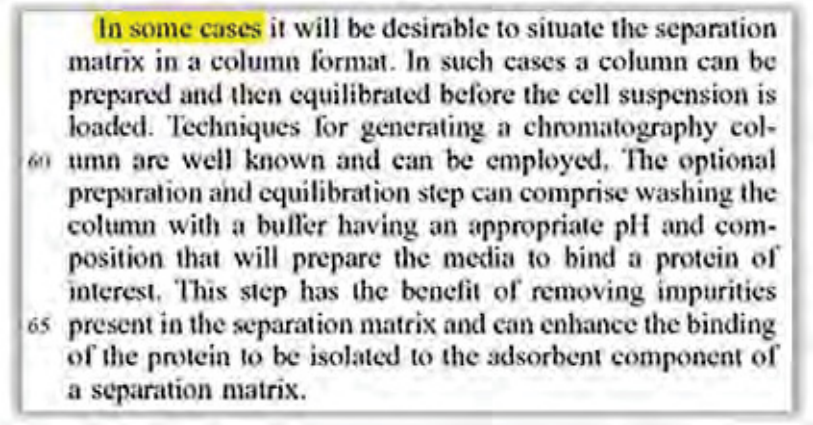
[31] Ex. 6, Non-Confidential Amgen Opening Appeal Brief ("Amgen Opening Appeal Br.") at 15, *Amgen Inc. v. Sandoz Inc.*, No. 18-1551 (Fed. Cir. Apr. 12, 2018) (ECF No. 29).

104. Second, the '997 patent specification confirms that "a column" is only a single embodiment for the separation matrix of the claims. For example:



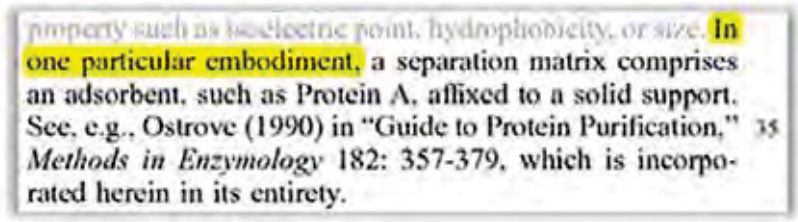
As noted, the separation matrix can be disposed in a column. The column can be run with or without pressure and from top to bottom or bottom to top. The direction of the flow of fluid in the column can be reversed during the purification process. Purifications can also be carried out using a batch process in which the solid support is separated from the liquid used to load, wash, and elute the sample by any suitable means, including gravity, centrifugation, or filtration. Moreover, purifications can also be carried out by contacting the sample with a filter that adsorbs or retains some molecules in the sample more strongly than others, such as anion exchange membrane chromatography.

('997 patent at col. 11, ll. 41-52 (emphasis added));



In some cases it will be desirable to situate the separation matrix in a column format. In such cases a column can be prepared and then equilibrated before the cell suspension is loaded. Techniques for generating a chromatography column are well known and can be employed. The optional preparation and equilibration step can comprise washing the column with a buffer having an appropriate pH and composition that will prepare the media to bind a protein of interest. This step has the benefit of removing impurities present in the separation matrix and can enhance the binding of the protein to be isolated to the adsorbent component of a separation matrix.

(*id.* at col. 16, ll. 56-67 (emphasis added)); and



property such as isoelectric point, hydrophobicity, or size. In one particular embodiment, a separation matrix comprises an adsorbent, such as Protein A, affixed to a solid support. See, e.g., Ostrove (1990) in "Guide to Protein Purification," *Methods in Enzymology* 182: 357-379, which is incorporated herein in its entirety.

(*id.* at col. 7, ll. 32-37 (emphasis added)).

105. Given the multiple disclosures I have illustrated above, it is my opinion that if the inventors intended for the claims to be limited to column chromatography, then they would have

expressly done so in the claims. Instead, the inventors, in my opinion, used the more general term, "separation matrix," to intentionally encompass non-column separation systems. Accordingly, it is my opinion that Amgen's proposed construction is inappropriate and inconsistent with the inventors' intent and how a person of ordinary skill in the art would understand the plain language of the Asserted Claims—particularly, in view of the express disclosures in the specification presenting column chromatography as just one embodiment.

106. Finally, it is also my opinion that Amgen's proposed construction is inconsistent with the parties' undisputed construction of the term "separation matrix," which is expressly defined in the '997 patent specification without any mention of a column. Yet, here, Amgen proposes that "separation matrix"—as it appears within the disputed claim term, "applying the refold solution to a separation matrix"—now means something different: "a column that contains the separation matrix." I disagree. In my opinion, a person of ordinary skill in the art would not apply different definitions of the same term appearing in different parts of a patent. Instead, in my opinion, a person of ordinary skill in the art would expect the *same* definition to apply each time a term appears in a patent.

* * *

107. For at least the reasons stated above, it is my opinion that "applying the refold solution to a separation matrix" should be construed consistent with the *Sandoz* Court's construction for "directly applying" from the '878 parent patent. In my opinion, a person of ordinary skill in the art would understand the terms to be synonymous—or, at the very least, have no substantive difference—and, moreover, would recognize Amgen's numerous disclosures and statements in the patent specification and prosecution history confirming that "applying" in the claims meant direct application. Nothing, in my opinion, warrants a new, different

construction for this term.

3. *under conditions suitable for the protein to associate with the matrix*

Disputed Claim Term or Phrase (in Bold)	Amgen's Proposal	Mylan's Proposal
(c) applying the refold solution to a separation matrix **under conditions suitable for the protein to associate with the matrix**;	under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment	"under conditions suitable for the protein to be purified to bind to the matrix" Ex. 2, *Sandoz* Order at 25-29

108. For the following reasons, I disagree with Amgen's proposal. In my opinion, the claim term should be construed in accordance with its plain and ordinary meaning as "under conditions suitable for the protein to be purified to bind to the matrix."

a. The *Sandoz* Court was correct.

109. In my opinion, the Court in *Amgen v. Sandoz* correctly construed this claim term as "under conditions suitable for the protein to be purified to bind to the matrix." (Ex. 2, *Sandoz* Order at 24-33). The keys to this construction, in my opinion, are that the Court correctly recognized: **(i)** that "the protein" of the claimed method referred to "the protein to be purified" and not just any protein (*see, e.g.*, *id.* at 26 ("[T]he method claimed is one of protein purification, and therefore all steps listed in the claim drive towards the purification of one specific protein."); *id.* ("The process of washing removes unwanted protein from the refold mixture, leaving only the sought-after protein stuck to the separation matrix.")); and **(ii)** that "associate with the matrix" under the claimed method would be understood by a person of ordinary skill in the art as "bind to the matrix" (*see, e.g.*, *id.* at 28 ("The patentee differentiated between proteins 'associated with' the separation matrices and those components and proteins 'unbound' from the matrices—a telling choice of words which implies the words are synonyms for the same process.") (citing the

'878 patent at col. 15, ll. 43-46 ("After the protein of interest has associated with the separation matrix[,] the separation matrix is washed to remove ***unbound protein***, lysate, impurities and unwanted components of the refold solution.") (emphasis added)); the '878 patent at col. 15, ll. 65-67 ("[t]he protein of interest can be eluted using a solution that interferes with the ***binding*** of the adsorbent component of the separation matrix to the protein.") (emphasis added)).[32]

b. Amgen's proposal incorrectly broadens the scope of the claimed method to just *any* "protein."

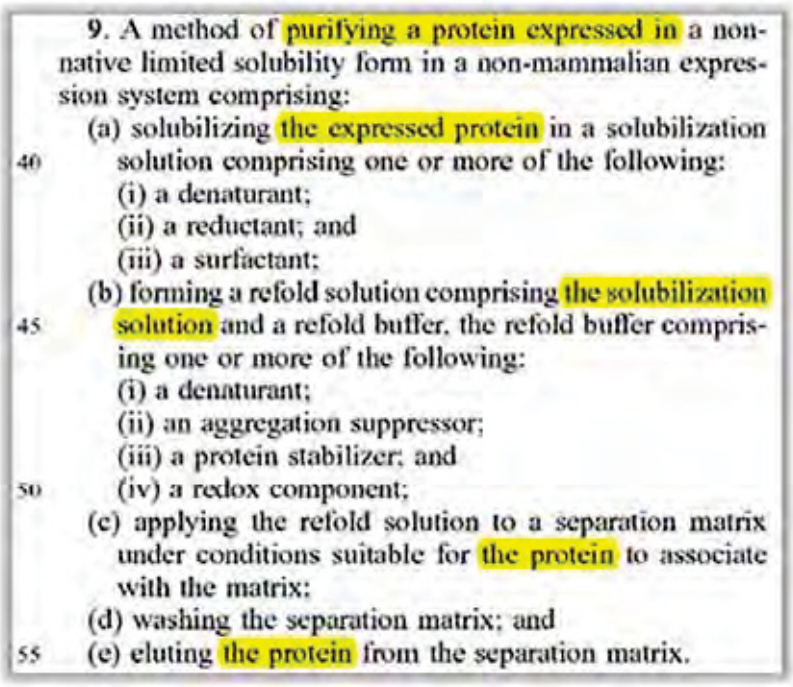
110. As the *Sandoz* Court noted, "Amgen believes the word 'protein' [in the claims] refers to ***any*** protein expressed by the non-mammalian expression system, not just the protein of interest, i.e., the recombinant protein expressed by the host cell." (Ex. 2, *Sandoz* Order at 25 (emphasis added)). For the following reasons, I agree with the *Sandoz* Court's conclusions that "the method claimed is . . . more targeted than Amgen suggested" and "[t]he targeted protein [of the claimed method] is ***the protein to be purified***." (*Id.* at 26 (emphasis added); *see also* '997 patent at col. 15, ll. 23-30 (disclosing that the "protein of interest" (i.e., the protein to be purified by the claimed method) is the specific protein that is applied to the separation matrix, not just any protein); *id.* at col. 15, ll. 50-67 (same); *id.* at col. 16, ll. 1-4 (same)).

111. First, in my opinion, a person of ordinary skill in the art would recognize, as the *Sandoz* Court stated, "that the method claimed is one of protein purification, and therefore all

[32] As I explain in greater detail below (*see* ¶¶ 127-35), Amgen's proposed construction for "washing the separation matrix," which requires that the wash solution have "the effect of removing unbound protein," is completely inconsistent with its proposal here for "associate" being more than just binding. If the protein to be purified is merely "interacting" with the separation matrix (i.e., is *unbound*), then, under Amgen's proposed construction for "washing the separation matrix," the unbound protein to be purified washed away with all the impurities. In other words, if Amgen's constructions are accepted, then the Asserted Claims will cover methods in which all the protein to be purified is lost during the wash step. In my opinion, this is a completely unacceptable (and indeed illogical) interpretation of the claim language.

steps listed in the claim drive towards the purification of one specific protein." (Ex. 2, *Sandoz* Order at 26). Under the Asserted Claims, that "one specific protein" is the "protein expressed in a non-native limited solubility form[33] in a non-mammalian expression system"—in other words, the protein to be purified.

112. Second, in my opinion, "the protein" of **step (c)** is very easily tracked by the plain language of the Asserted Claims to the protein expressed and purified under the claimed method:



9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
(i) a denaturant;
(ii) a reductant; and
(iii) a surfactant;
(b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
(i) a denaturant;
(ii) an aggregation suppressor;
(iii) a protein stabilizer; and
(iv) a redox component;
(c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
(d) washing the separation matrix; and
(e) eluting the protein from the separation matrix.

('997 patent at col. 22, ll. 36-55 (emphasis added)). As illustrated in the above highlighted claim 9, the preamble establishes that method is directed toward "purifying" a specific protein: "a protein expressed in a non-native limited solubility form in a non-mammalian expression system." Each subsequent reference to "protein" in the claimed method is preceded by a definite article, "the." In my opinion, a person of ordinary skill in the art would read each "the []

[33] To a person of ordinary skill in art, the phrase "in a non-native limited solubility form" further clarifies the target protein of the claimed method and confirms that "the protein" cannot simply be any protein expressed by a non-mammalian organism. (*See* ¶ 111 below).

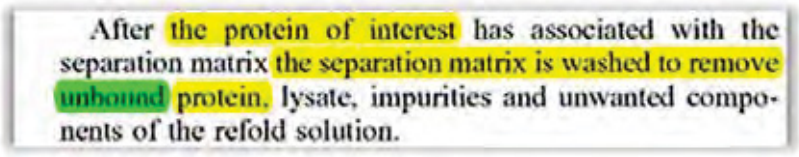
protein" as referring back to the "protein" term recited earlier in the claim. In other words:

- "***the*** protein" from **step (e)** is "***the*** protein" from **step (c)**, which is bound to the separation matrix in step (c) and washed in step (d);
- "***the*** protein" from **step (c)** is "***the*** expressed protein" from **step (a)**, which is solubilized in a solubilization solution in step (a), and then added to a refold buffer to form a refold solution in step (b); and
- "***the*** expressed protein" from **step (a)** is the "protein expressed in a non-native limited solubility form in a non-mammalian expression system" from the preamble, which is ultimately purified under the claimed method—i.e., "the protein to be purified."

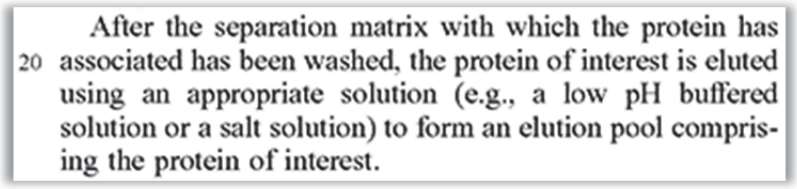
In sum, these steps describe a method targeting a specific protein (not just any protein) to be purified by the claimed method—no other protein (e.g., a host cell protein or impurity) is addressed by the claimed method.

c. The term "associate with the matrix" is very well-understood to a person of ordinary skill in the art.

113. In my opinion, the phrase "associate with the matrix" as it appears in the disputed claim term would be well understood by a person of ordinary skill in the art to mean bind to the matrix. Specifically, the claimed method is expressly a "capture purification" method and, indeed, the steps of the claimed method (e.g., applying to a separation matrix, washing and eluting) are consistent with a capture purification system. Thus, within the context of the Asserted Claims, it is my opinion that a person of ordinary skill in the art would know that the "conditions suitable" must allow for the "protein to be purified" to be retained (i.e., bound) on the separation matrix so that it may be **washed** and subsequently **eluted**. For example, the '997 patent specification provides:


After the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution.

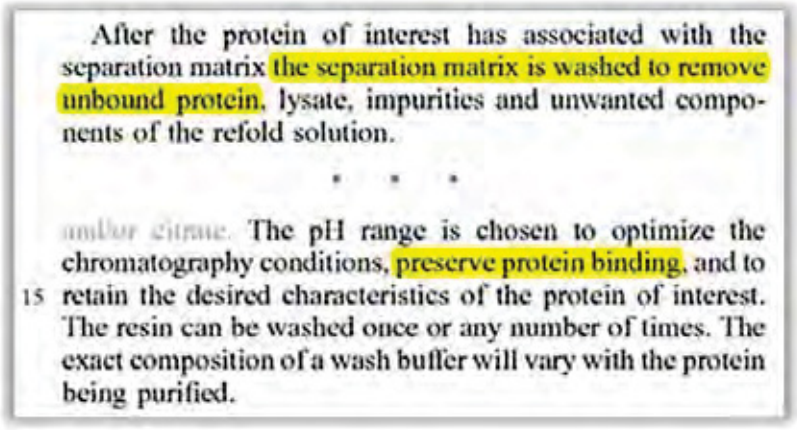
('997 patent at col. 16, ll. 1-5 (emphasis added)); and



After the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution (e.g., a low pH buffered solution or a salt solution) to form an elution pool comprising the protein of interest.

(*id.* at col. 16, ll. 19-23)[34].

114. If the "protein to be purified" is not bound to the matrix, it can flow through in the eluate and/or get washed out with all the other unbound protein, impurities and unwanted components. In contrast, the '997 patent specification expressly discloses that the wash buffer be chosen to "preserve protein ***binding***" of the protein being purified while simultaneously "remov[ing] ***unbound*** protein":



After the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution.

* * *

amber citrate. The pH range is chosen to optimize the chromatography conditions, preserve protein binding, and to retain the desired characteristics of the protein of interest. The resin can be washed once or any number of times. The exact composition of a wash buffer will vary with the protein being purified.

('997 patent at col. 16, ll. 1-18 (emphasis added)). Again, these disclosures are consistent with how a person of ordinary skill in the art would understand a capture purification method.

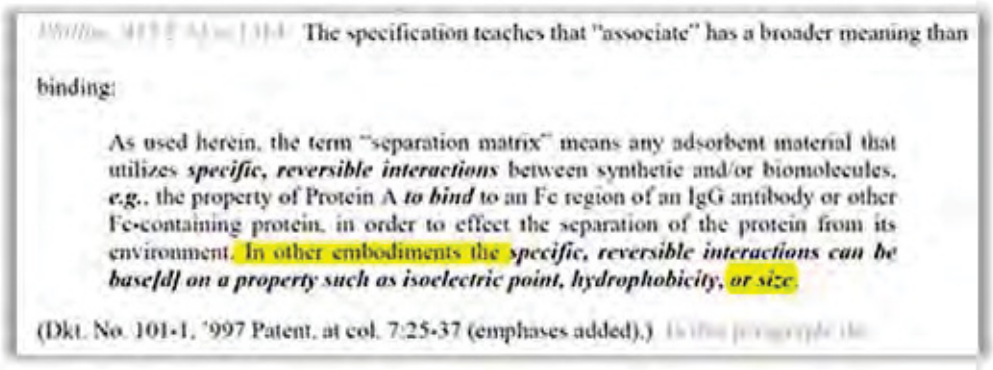
115. Moreover, the '997 patent repeatedly uses the term "associate" in the context of protein *binding* to the separation matrix. (*See, e.g.*, '997 patent at col. 1, ll. 33-40; *id.* at col. 1, ll.

[34] A person of ordinary skill in the art would know that "a low pH buffered solution or a salt solution" is a well-known way of eluting bound protein from a separation matrix.

41-51; *id.* at col. 4, ll. 60-66; *id.* at col. 5, ll. 10-14; *id.* at col. 8, ll. 25-48; *id*. at col. 10, ll. 16-26; *id.* at col. 10, ll. 45-50; *id.* at col. 10, l. 64-col. 11, l. 3; *id.* at col. 15, ll. 23-30; *id.* at col. 15, ll. 60-67; *id.* at col. 16, ll. 1-4; *id.* at col. 16, ll. 19-23). In comparison, the '997 patent specification uses the phrase "reversible interactions" in a single paragraph that defines the term "separation matrix" without any connection to the term "associate."

d. Amgen incorrectly relies on the patent's definition of "separation matrix" as a definition of "associate."

116. In support of its proposed construction, Amgen cites only the disclosure in the '997 patent specification where the named inventors defined the term "separation matrix":



The specification teaches that "associate" has a broader meaning than binding:

> As used herein, the term "separation matrix" means any adsorbent material that utilizes ***specific, reversible interactions*** between synthetic and/or biomolecules, ***e.g.***, the property of Protein A ***to bind*** to an Fc region of an IgG antibody or other Fc-containing protein, in order to effect the separation of the protein from its environment. In other embodiments the ***specific, reversible interactions can be base[d] on a property such as isoelectric point, hydrophobicity, or size***.

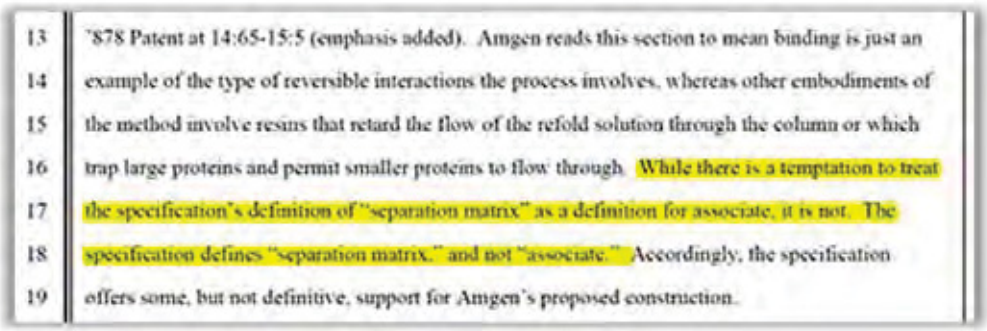
(Dkt. No. 101-1, '997 Patent, at col. 7:25-37 (emphases added).)

(Amgen Br. at 18 (emphasis added)). In my opinion, the '997 patent's definition of "separation matrix" is **(i)** not relevant to the meaning of "associate" within the Asserted Claims, and **(ii)** directed toward "other embodiments" that do not fall within the scope of the Asserted Claims, e.g., size exclusion.

(i) *The '997 patent does not teach or define the claim term, "associate with" as "reversible interaction."*

117. As I stated above (*see* ¶ 115), the '997 patent repeatedly uses the term "associate" in the context of protein *binding* to the separation matrix. While, by comparison, the '997 patent specification uses the phrase "reversible interactions" in a single paragraph that defines the term "separation matrix" without any connection to the term "associate." Accordingly, I agree with

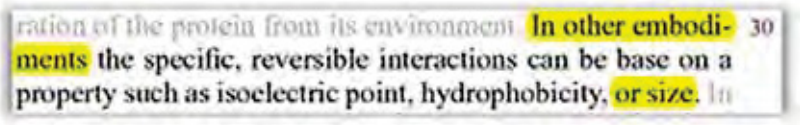
the *Sandoz* Court's conclusion that the '997 patent specification only "defines 'separation matrix,' and not 'associate'":


'878 Patent at 14:65-15:5 (emphasis added). Amgen reads this section to mean binding is just an example of the type of reversible interactions the process involves, whereas other embodiments of the method involve resins that retard the flow of the refold solution through the column or which trap large proteins and permit smaller proteins to flow through. While there is a temptation to treat the specification's definition of "separation matrix" as a definition for associate, it is not. The specification defines "separation matrix," and not "associate." Accordingly, the specification offers some, but not definitive, support for Amgen's proposed construction.

(Ex. 2, *Sandoz* Order at 27 (emphasis added)).

(ii) ***Non-binding embodiments that do not involve washing and elution step (e.g., size exclusion) are <u>not</u> within the scope of the claims.***

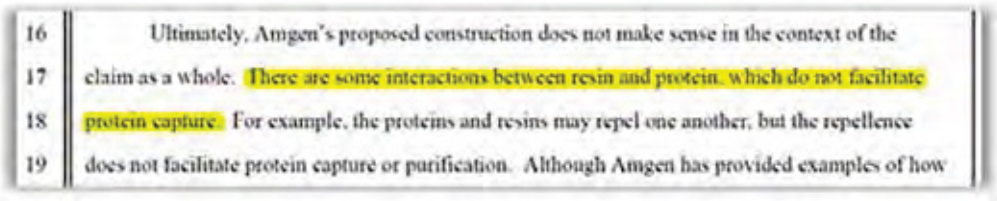
118. Separately, I disagree with Amgen's reliance on the paragraph of the '997 patent appearing at col. 7, ll. 25-37 as support for its argument that "associate" in the Asserted Claims must mean "reversible interactions," and not just "binding," because the specification teaches other, specific, reversible interactions that do not involve binding. (*See* Amgen Br. at 17-18 (citing only the '997 patent at col. 7, ll. 25-37)). I understand Amgen's argument to rely upon the following disclosure:


ration of the protein from its environment. In other embodiments the specific, reversible interactions can be base on a property such as isoelectric point, hydrophobicity, or size. In

('997 patent at col. 7, ll. 30-32 (emphasis added)). As Amgen points out, interactions based on "size" do not involve binding. However, Amgen is *incorrect* in relying on this statement in the specification to alter the plain and ordinary meaning of the word "associate" in the context of the Asserted Claims, which are specifically directed toward, and indeed comprise steps consistent with, a capture purification system. Size exclusion is **<u>not</u>** a capture purification. Therefore, in

my opinion, this disclosure is directed toward "other embodiments" of the disclosed methods but not necessarily all embodiments that fall within the scope of the Asserted Claims.

119. As the *Sandoz* Court recognized, not all interactions are consistent with capture purification:



> Ultimately, Amgen's proposed construction does not make sense in the context of the claim as a whole. There are some interactions between resin and protein, which do not facilitate protein capture. For example, the proteins and resins may repel one another, but the repellence does not facilitate protein capture or purification. Although Amgen has provided examples of how

(Ex. 2, *Sandoz* Order at 28). In my opinion, a person of ordinary skill in the art knows that size exclusion is a chromatography method that does not involve protein capture. Instead, size exclusion chromatography separates proteins according to size and is well known in the art as follows:

> [s]ize exclusion chromatography; also called gel filtration … separates proteins according to size. The column contains a cross-linked polymer with pores of selected size. Larger proteins migrate faster than smaller ones, because they are too large to enter the pores in the beads and hence take a more direct route through the column. The smaller proteins enter the pores and are slowed by the more labyrinthian path they take through the column.

(Ex. 11, Principles of Biochemistry[35] at 139); and

> [t]his technique separates proteins on the basis of size and shape. The beads used for this type of chromatography do not have charged chemical groups attached. Instead, each bead has a variety of different-sized pores penetrating their surface. … Small proteins can enter all the pores and therefore can access more of the column and take longer to elute (in other words, they have more space to explore). Large proteins can access less of the column and elute more rapidly.

(Ex. 12, Molecular Biology of the Gene[36] at 766-67). In other words, the proteins are not

[35] Principles of Biochemistry refers to ALBERT L. LEHNINGER ET AL., PRINCIPLES OF BIOCHEMISTRY (2d ed. 1993).

captured to achieve purification.

120. It is also well-known in the art that size exclusion chromatography does not include separate wash and elution steps—*required* steps of the Asserted Claims. Indeed, in my opinion, adding extra buffer (consistent with a wash step) would completely defeat the purpose of a size exclusion method.

121. For at least the reasons I have described above, I disagree with Amgen's construction of "associate" to mean "reversible interactions."

e. Dr. Willson's *Amgen v. Sandoz* declaration confirms my opinion that a person of ordinary skill in the art would understand "associate" in the Asserted Claims to mean "bind."

122. I have been asked to review Dr. Willson's previous declaration from the *Amgen v. Sandoz* matter to evaluate whether Amgen's current proposed construction for "associate" is consistent with his prior opinions. As I explain in the following paragraphs, Dr. Willson's prior declaration **(i)** contradicts Amgen's current proposal, and **(ii)** confirms my opinion that a person of ordinary skill in the art would understand "associate" in the Asserted Claims to mean "bind."

123. In the following table, I present a side-by-side comparison of several paragraphs from the technological background sections of Dr. Willson's declarations submitted in the respective *Amgen v. Sandoz* matter and the current matter. As seen, while the majority of the language in these paragraphs remained identical, Dr. Willson simply replaced all references to protein *binding* to the separation matrix (highlighted in **blue**) to *interacting* with the separation matrix (highlighted in **red**):

[36] Molecular Biology of the Gene refers to JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE (Beth Wilbur et al. eds., 6th ed. 2008).

Dr. Willson's *Amgen v. Sandoz* Decl.[37]	Dr. Willson's Current Decl.
¶105: Ion-exchange chromatography takes advantage of differences in the type and strength of ionic interactions of the different molecules in a sample with a charged resin. Negatively-charged molecules can **bind** resins carrying positively-charged groups (anion-exchange chromatography, or AEX) and positively charged molecules can **bind** resins carrying negatively charged groups (cation-exchange chromatography, or CEX)	**¶49:** Ion-exchange chromatography takes advantage of differences in the type and strength of ionic interactions of the different molecules in a sample with a charged resin. Negatively-charged molecules can **interact with, including binding to,** resins carrying positively-charged groups (anion-exchange chromatography, or AEX) and positively charged molecules can **interact with, including binding to,** resins carrying negatively charged groups (cation-exchange chromatography, or CEX)
¶107: Generally, proteins **bind** best **to** IEX resins at low salt concentrations and **unbind** as the salt concentration increases. High concentrations of salt ions shield the charges on the resin and the protein from each other, reducing their interactions. At low salt concentrations, charges on the stationary phase remain unshielded and allow proteins and other molecules with the opposite charge to **bind**.	**¶50:** Generally, proteins **interact** best **with** IEX resins at low salt concentrations and the **interaction between the protein and the resin will be reversed** as the salt concentration increases. High concentrations of salt ions shield the charges on the resin and the protein from each other, reducing their interactions. At low salt concentrations, charges on the stationary phase remain unshielded and allow proteins and other molecules with the opposite charge to **interact**.
¶108: In addition to separating proteins and other molecules according to the sign of their net charge, i.e., positive or negative, IEX can also separate proteins and other molecules according to the strength of their ionic interactions to the charged resin. More negatively charged molecules, for example, can have stronger ionic interactions with a positively charged resin than their less negatively charged counterparts and thus **remain bound** to the column longer. The spatial distribution of charges on a protein can influence **binding**, as well. In fact, proteins often adsorb on strong anion exchange	**Omitted.**

[37] Ex. 3, Declaration of Richard C. Willson in Support of Amgen's Brief in Opposition to Sandoz's Motion for Summary Judgment on Noninfringement, *Amgen Inc. et al. v. Sandoz Inc. et al.*, No. 14-cv-04741-RS, No. 16-cv-02581 (N.D. Cal. Nov. 13, 2017) (ECF No. 291-1).

resins . . . even at their isoelectric points, because while the net charge is zero, surface charges or groups of charges can mediate **binding**. Lastly, proteins in different folding states, or conformations, can differ in the strength of their ionic interactions to the charged resin, even if the protein has the same amino acid sequence.	
¶109: Elution can occur by changing the properties of the mobile phase to increase the concentration of ionic species, which competitively displace **the bound protein**. A change in pH can also result in elution, due to changes in the charge of the adsorbed protein and its **binding capacity**.	**¶51:** Elution can occur by changing the properties of the mobile phase to increase the concentration of ionic species, which **can** competitively displace **the adsorbed proteins**. A change in pH can also result in elution, due to changes in the charge of the adsorbed protein and its **propensity to interact with the resin. These changes may be induced by changing the composition of liquid entering the column, or they may be generated internally in a column being fed a liquid of constant composition**.

124. First, I strongly disagree with Dr. Willson's changes from **binding** (for the '878 patent) to **interacting with** (for the '997 patent) in his respective declarations. Nothing in the '997 patent warrants these substitutions. Indeed, as I stated above, it is my understanding that the '878 patent is parent to the '997 patent and both share the same specification—plus, several claims are nearly identical (*e.g.*, *compare* '878 patent (claim 7), *with* '997 patent (claim 9)); and therefore, it is my understanding and opinion that the technological background for each patent would be the same to a person of ordinary skill in the art.

125. Second, Dr. Willson's original declaration supports and confirms my opinion that, under the Asserted Claims, the protein to be purified must *bind* to the separation matrix. That is the plain and ordinary meaning of "associate" in the context of the '878 and '997 patents.

* * *

126. For at least the reasons I have stated above, it is my opinion that "under

conditions suitable for the protein to associate with the matrix" should be construed in accordance with its plain and ordinary meaning and consistent with the *Sandoz* Court's construction of the identical claim term as "under conditions suitable for the protein to be purified to bind to the matrix."

4. *washing the separation matrix*

Disputed Claim Term or Phrase (in Bold)	Amgen's Proposal	Mylan's Proposal
(d) **washing the separation matrix**; and	applying a solution to the column that contains the separation matrix, which application has the effect of removing unbound protein, lysate, impurities, and unwanted components of the refold solution from the separation matrix while preserving interactions between the protein and the separation matrix	"applying a solution to remove unbound protein, lysate, impurities, and unwanted components of the refold solution from the separation matrix while preserving binding of the expressed protein" Ex. 2, *Sandoz* Order at 29-30

127. For the following reasons, I disagree with Amgen's proposal. In my opinion, the claim term should be construed in accordance with its plain and ordinary meaning as "applying a solution to remove unbound protein, lysate, impurities, and unwanted components of the refold solution from the separation matrix while preserving binding of the expressed protein."

a. The *Sandoz* Court was correct.

128. As an initial matter, I note that the *Sandoz* Court provided two constructions for this claim term in its Order. (*Compare* "adding a solution to the separation matrix to remove materials in the refold solution while preserving binding of the protein to be purified", *with* "[a]pplying a solution to remove unbound protein, lysate, impurities, and unwanted components of the refold solution from the separation matrix while preserving binding of the expressed

protein"). In either construction, however, the Court recognized what, in my opinion, is the absolute key to correctly construing this term: that a person of ordinary skill in the art would understand "washing the separation matrix" to require **(i)** "remov[ing] ***unbound*** protein" (among other things) **(ii)** "while preserving ***binding***" of the protein to be purified (i.e., the expressed protein / protein of interest that is to be purified by the claimed method). Indeed, as I explain above, the claimed method is a capture purification, which is specifically understood by a person of ordinary skill the art to *bind* the protein to be purified to a matrix and thus separate *bound* protein from *unbound* protein. Accordingly, I believe the *Sandoz* Court was correct. Moreover, I understand that Amgen has not disputed the *Sandoz* Court's construction of this identical claim term. (Ex. 6, Amgen Opening Appeal Br. at 28). ("The district court construed 'washing the separation matrix' to mean "adding a solution to the separation matrix to remove materials in the refold solution while preserving binding of the protein to be purified.").

129. In my opinion, the *Sandoz* Court correctly construed this claim term as "under conditions suitable for the protein to be purified to bind to the matrix." (Ex. 2, *Sandoz* Order at 25-31).

b. The Asserted Claims are not limited to column chromatography.[38]

130. Like its proposed construction for "applying the refold solution to a separation matrix," I understand Amgen's proposal for "washing the separation matrix" as another attempt to limit the method of the Asserted Claims to column chromatography. As I explained above, neither the plain language of the claims nor the patent specification support reading in such a

[38] I must point out that neither Amgen nor Dr. Willson provides any explanation or evidence to support limiting the claimed method to column chromatography in their opening submissions. Accordingly, I expressly reserve the right to submit a reply in the event Amgen or Dr. Willson submits any evidence or argument in their next submissions.

limitation. In fact, the '997 patent specification provides express disclosures that, in my opinion, inform a person of ordinary skill in the art that column chromatography is just one embodiment of the Asserted Claims. (*See, e.g.*, '997 patent at col. 11, ll. 41-52 ("[T]he separation matrix ***can be*** disposed in a column . . . . Purifications can also be carried out using a batch process in which the solid support is separated from the liquid . . . by any suitable means, including gravity, centrifugation, or filtration.") (emphasis added); *id.* at col. 16, ll. 56-67 ("***In some cases*** it will be desirable to situate the separation matrix in a column format.") (emphasis added)). I understand the *Sandoz* Court reached the same conclusion: "The claim shall not be limited to the column method of chromatography." (Ex. 2, *Sandoz* Order at 29).

131. This is one more reason why I disagree with Amgen's proposal.

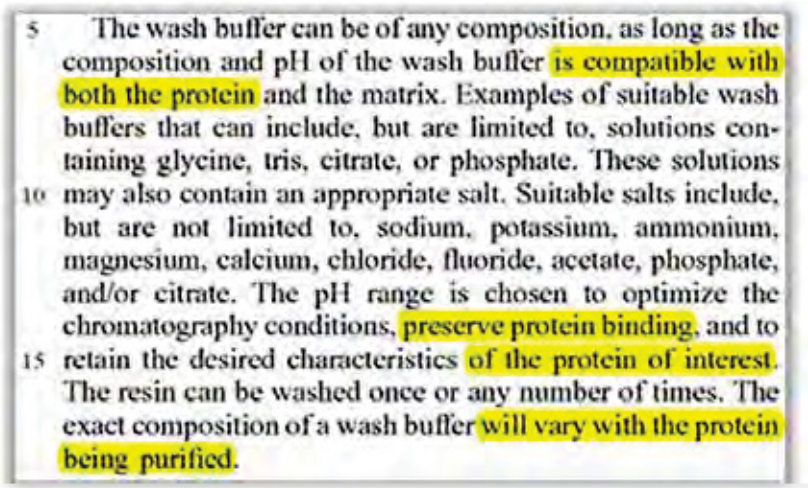
c. Under the Asserted Claims, proteins "bind" to the separation matrix when they "associate" with it, and thus, washing removes unbound protein and preserves binding of the protein to be purified.

132. Like its proposed construction for "under conditions suitable for the protein to associate with the matrix," I understand Amgen's proposal for "washing the separation matrix" as another attempt to change the meaning of "associate" in the Asserted Claims from "bind" (which Amgen agreed to for the '878 parent patent, *see* ¶¶ 116-20 above) to "interact."

133. As I explained above (*see* ¶¶ 113-14), a person of ordinary skill in the art would understand "associate with the matrix"—as that term appears in the Asserted Claims—to mean "bind with the matrix," in accordance with the claim term's plain and ordinary meaning. I understand the *Sandoz* Court reached the same conclusion in construing "washing the separation matrix": "[T]he proteins ***bind*** to the separation matrix when they 'associate' with it." (Ex. 2, *Sandoz* Order at 29 (emphasis added)). I agree.

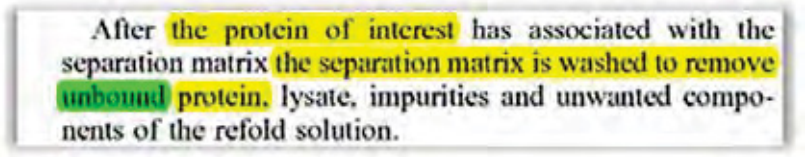
134. Moreover, the '997 patent provides disclosures relating to the wash and wash

buffer of the claimed method that, in my opinion, expressly confirms that washing the separation matrix under the Asserted Claims "preserve[s] protein binding" of the protein to be purified:



The wash buffer can be of any composition, as long as the composition and pH of the wash buffer is compatible with both the protein and the matrix. Examples of suitable wash buffers that can include, but are limited to, solutions containing glycine, tris, citrate, or phosphate. These solutions may also contain an appropriate salt. Suitable salts include, but are not limited to, sodium, potassium, ammonium, magnesium, calcium, chloride, fluoride, acetate, phosphate, and/or citrate. The pH range is chosen to optimize the chromatography conditions, preserve protein binding, and to retain the desired characteristics of the protein of interest. The resin can be washed once or any number of times. The exact composition of a wash buffer will vary with the protein being purified.

('997 patent at col. 16, ll. 5-18 (emphasis added));



After the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution.

(*id.* at col. 16, ll. 1-5 (emphasis added)).

135. This is an additional reason why I disagree with Amgen's proposal.

* * *

136. For at least the reasons I have stated above, it is my opinion that "washing the separation matrix" should be construed in accordance with its plain and ordinary meaning and consistent with the *Sandoz* Court's construction(s) of the identical claim term as "applying a solution to remove unbound protein, lysate, impurities, and unwanted components of the refold

solution from the separation matrix while preserving binding of the expressed protein."[39]

5. *eluting the protein from the separation matrix*

Disputed Claim Term or Phrase (in Bold)	Amgen's Proposal	Mylan's Proposal
(e) **eluting the protein from the separation matrix**	applying a solution to the column that contains the separation matrix, which application has the effect of reversing the interactions between the protein and the separation matrix	"applying a solution that reverses the binding of the purified protein to the separation matrix" This step must occur after the step of "washing the separation matrix." Ex. 2, *Sandoz* Order at 30-31

137. For the following reasons, I disagree with Amgen's proposal. In my opinion, the claim term should be construed in accordance with its plain and ordinary meaning as "applying a solution that reverses the binding of the purified protein to the separation matrix." Moreover, in my opinion, the elution step of the Asserted Claims would be immediately understood by a person of ordinary skill in the art as a separate step that must occur *after* the "washing the separation matrix" step.

a. The *Sandoz* Court was correct.

138. Again, the *Sandoz* Court was presented with an identical claim term for construction. In my opinion, the Court in *Amgen v. Sandoz* correctly construed this claim term as "[a]pplying a solution that reverses the binding of the purified protein to the separation matrix." (Ex. 2, *Sandoz* Order at 33). I agree with the *Sandoz* Court's construction, because,

[39] In my opinion, the *Sandoz* Court's other construction ("adding a solution to the separation matrix to remove materials in the refold solution while preserving binding of the protein to be purified") is equally acceptable for the reasons I have stated above.

again, in my opinion, the Court recognized the keys to properly construing this term from the perspective of a person of ordinary skill in the art: **(i)** that the plain and ordinary meaning of elution (or eluting) is to reverse the ***binding*** of the purified protein to the separation matrix; and **(ii)** that elution in a capture purification method is well-known and understood to be a separate and distinct step from washing, involving a different solution—in other words, the wash solution is specifically designed to preserve binding of the protein to be purified, whereas the elution solution is specifically designed to reverse *that* protein binding. I further understand that Amgen has not challenged the *Sandoz* Court's construction of this identical claim term. (Ex. 6, Amgen Opening Appeal Br. at 38-39).

b. The Asserted Claims are not limited to column chromatography.[40]

139. Like its proposed constructions for "applying the refold solution to a separation matrix" and "washing the separation matrix," I understand Amgen's proposal for "eluting the protein from the separation matrix" as another attempt to limit the method of the Asserted Claims to column chromatography. As I explained above, neither the plain language of the claims nor the patent specification support reading in such a limitation.

c. Under the Asserted Claims, proteins "bind" to the separation matrix when they "associate" with it, and thus, eluting reverses the *binding* of the purified protein.

140. Like its proposed constructions for "under conditions suitable for the protein to associate with the matrix" and "washing the separation matrix," I understand Amgen's proposal for "eluting the protein from the separation matrix" as another attempt to change the meaning of

[40] Again, I must point out that neither Amgen nor Dr. Willson provides any explanation or evidence to support limiting the claimed method to column chromatography in their opening submissions. Accordingly, I expressly reserve the right to submit a reply in the event Amgen or Dr. Willson submits any evidence or argument in their next submissions.

"associate" in the Asserted Claims from "bind" (which Amgen agreed to for the '878 parent patent, *see* ¶¶ 132-35 above) to "interact."

141. As I explained above (*see* ¶¶ 113-14), a person of ordinary skill in the art would understand "associate with the matrix"—as that term appears in the Asserted Claims—to mean "bind with the matrix," in accordance with the claim term's plain and ordinary meaning. I understand the *Sandoz* Court reached the same conclusion: "[T]he proteins ***bind*** to the separation matrix when they 'associate' with it." (Ex. 2, *Sandoz* Order at 29 (emphasis added)). I agree.

142. Moreover, the '997 patent provides a disclosure relating to the elution step of the claimed method that, in my opinion, expressly confirms that eluting the protein from the separation matrix under the Asserted Claims reverses the binding of the protein to be purified:

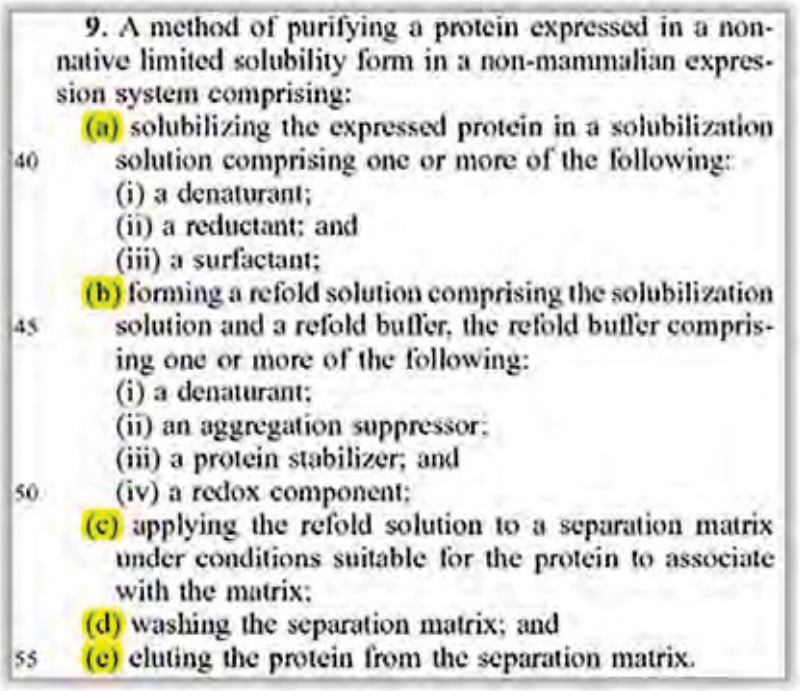
> The protein of interest can be eluted using a solution that interferes with the binding of the adsorbent component of the separation matrix to the protein, for example by disrupting the interactions between Protein A and the Fc region of a protein of interest. This solution may include an agent that can either increase or decrease pH, and/or a salt. In various embodiments, the elution solution can comprise acetic acid, glycine, or citric acid. Elution can be achieved by lowering the pH. For example, the pH can be lowered to about 4.5 or less, for example to between about 3.3 to about 4.2 (e.g., 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1 or 4.2, using a solution comprising citrate or acetate, among other possibilities.

('997 patent at col. 16, ll. 24-35 (emphasis added)). I understand the *Sandoz* Court reached the same conclusion in construing the identical claim term: "elution involves cleaving the protein from the matrix with 'a solution *that interferes with the binding* of the absorbent [sic] component of the separation matrix to the protein, for example by *disrupting the interactions* between Protein A and the Fc region of a protein of interest.'" (Ex. 2, *Sandoz* Order at 31).

d. Asserted Claims expressly require the steps be performed in the order written.

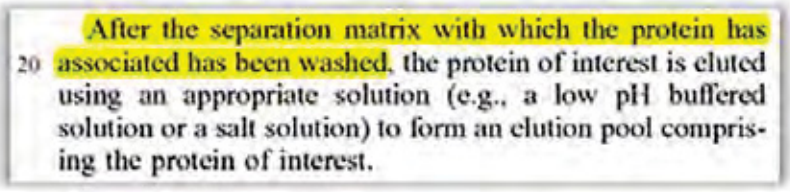
143. Finally, in my opinion, a person of ordinary skill in the art would understand the

Asserted Claims as expressly requiring the itemized steps be performed in the order written. More specifically, the steps in the claims are expressly labeled in sequential order from (a) to (e):



9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
(i) a denaturant;
(ii) a reductant; and
(iii) a surfactant;
(b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
(i) a denaturant;
(ii) an aggregation suppressor;
(iii) a protein stabilizer; and
(iv) a redox component;
(c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
(d) washing the separation matrix; and
(e) eluting the protein from the separation matrix.

('997 patent at col. 22, ll. 36-55 (emphasis added)). The same express, sequential order is provided in the specification. (*See, e.g.*, *id.* at col. 2, ll. 21-37; *id.* at col. 20, ll. 4-8 (Example 2) ("***After*** loading, the column was washed with 25 mM Tris, 100 mM sodium chloride; pH 7.4 . . . The protein of interest was recovered from the resin with 100 mM sodium acetate, pH 3.7 [i.e., a completely different solution]." (emphasis added))). Moreover, the '997 patent specification confirms that the elution step under the Asserted Claims is separate, and occurs *after*, the washing step:



After the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution (e.g., a low pH buffered solution or a salt solution) to form an elution pool comprising the protein of interest.

(*Id.* at col. 16, ll. 19-23 (emphasis added)).

144. In my opinion, the only logical interpretation of the Asserted Claims is that the steps must be performed in order, including that the wash and elution are separate and sequential. I understand the *Sandoz* Court reached the same conclusion:

> the specification discloses a natural, logical order of steps. If the washing and eluting steps occurred simultaneously, the protein captured by the separation matrix could once again comingle with the contaminants and components to be washed away . . . . [T]he construction of the phrase will make clear the step of "eluting the protein from the separation matrix" occurs after the step of "washing the separation matrix."

(Ex. 2, *Sandoz* Order at 31). I agree with the *Sandoz* Court's description. In my opinion, a person of ordinary skill in the art would know that washing *after* eluting would not be scientifically feasible. There would be no protein remaining after elution to "wash;" just as if elution began before washing was completed, in capture purification, the protein would fail to be separated from the impurities.

* * *

145. For at least the reasons I have stated above, it is my opinion that "eluting the protein from the separation matrix" should be construed in accordance with its plain and ordinary meaning and consistent with the *Sandoz* Court's construction of the identical claim term as "applying a solution that reverses the binding of the purified protein to the separation matrix."

IX. RESERVATION OF RIGHTS

146. I reserve the right to supplement and/or expand upon my opinions in this declaration based on the information I have reviewed and/or based on any additional information that may be discovered, the Court's claim construction, or other circumstances that may impact my opinions.

147. At any trial or hearing, I may rely on materials and documents produced in the litigation, publicly available documents, and/or documents the parties have exchanged, such as

interrogatory responses. I also may rely on visual aids and/or demonstrative exhibits that I may prepare or have prepared based on my opinions.

I declare under penalty of perjury under the laws of the United States, that the foregoing is true and correct.

Dated: June 29, 2018

George Georgiou, Ph.D.